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(12) **United States Patent**
Anderson et al.(10) **Patent No.:** **US 9,233,998 B2**
(45) **Date of Patent:** **Jan. 12, 2016**(54) **NATURAL PRODUCT ANALOGS INCLUDING AN ANTI-INFLAMMATORY CYANOENONE PHARMACORE AND METHODS OF USE**(75) Inventors: **Eric Anderson**, Houston, TX (US);
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C07J 71/00 (2006.01)(52) **U.S. Cl.**CPC **C07J 41/0094** (2013.01); **C07C 255/46** (2013.01); **C07D 311/74** (2013.01); **C07D 317/26** (2013.01); **C07D 493/10** (2013.01); **C07F 7/1856** (2013.01); **C07J 21/003** (2013.01); **C07J 41/0055** (2013.01); **C07J 53/001** (2013.01); **C07J 71/0005** (2013.01); **C07C 2101/16** (2013.01)(58) **Field of Classification Search**USPC 558/440; 549/200
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**3,013,010 A 2/1957 Cardenas
2,875,201 A 2/1959 Johns 260/239.55
4,395,423 A 7/1983 Neumann 424/304
4,808,614 A 2/1989 Hertel 514/455,002,939 A 3/1991 Streber
5,013,649 A 5/1991 Wang et al. 435/69.1
5,064,823 A 11/1991 Lee et al. 514/198
5,401,838 A 3/1995 Chou 536/281
5,426,183 A 6/1995 Kjell 536/285.5
5,464,826 A 11/1995 Grindey et al. 514/50
5,521,294 A 5/1996 Wildfeuer 536/187
5,597,124 A 1/1997 Kessel et al. 241/30
5,603,958 A 2/1997 Morein et al. 424/489
5,606,048 A 2/1997 Chou et al. 536/271.1
5,629,295 A 5/1997 Deninno et al. 514/26
5,972,703 A 10/1999 Long et al. 435/372
6,025,395 A 2/2000 Breitner et al. 514/570
6,303,569 B1 10/2001 Greenwald et al. 514/2
6,326,507 B1 12/2001 Gribble et al. 558/415
6,369,101 B1 4/2002 Carlson 514/169
6,485,756 B1 11/2002 Aust et al. 424/725
6,552,075 B2 4/2003 Gribble et al. 514/522
6,642,217 B2 11/2003 Krasutsky et al. 514/169
6,649,654 B1 11/2003 Karin et al.

(Continued)

FOREIGN PATENT DOCUMENTSCN 1687021 A 10/2005
CN 102070697 5/2010

(Continued)

OTHER PUBLICATIONSNguyen et al., "Synthesis of the 5-7-6 Core of Guanacastepenes. Construction of C8 Quaternary Carbon via the Inversion of Stereochemistry." *Organic Letters*, vol. 4, No. 22, pp. 3959-3962, 2002.*

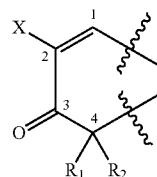
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ABSTRACT

This invention provides novel compounds comprising the following anti-inflammatory pharmacore:

wherein X, R₁ and R₂ are defined herein. Also provided are pharmaceutical compositions, kits and articles of manufacture comprising such compounds, methods and intermediates useful for making the compounds, and methods of using the compounds and compositions.**3 Claims, 24 Drawing Sheets**

(56)

References Cited

FOREIGN PATENT DOCUMENTS

U.S. PATENT DOCUMENTS

6,689,787	B1	2/2004	McKearn et al.	514/275
6,951,847	B2	10/2005	Gibson et al.	514/169
6,974,801	B2	12/2005	Honda et al.	514/25
6,991,814	B2	1/2006	Ray et al.	424/756
7,053,119	B2	5/2006	Karin et al.	
7,144,875	B2	12/2006	Gibson et al.	514/169
7,176,237	B2	2/2007	Honda et al.	514/519
7,265,096	B2	9/2007	Gallop et al.	514/49
7,288,568	B2	10/2007	Gribble et al.	514/519
7,399,606	B2	7/2008	Karin et al.	
7,410,958	B2	8/2008	Krasutsky et al.	514/169
7,435,755	B2	10/2008	Konopleva et al.	514/510
7,678,830	B2	3/2010	Honda et al.	
7,795,305	B2	9/2010	Konopleva et al.	
7,863,327	B2	1/2011	Gribble et al.	
7,915,402	B2	3/2011	Anderson et al.	540/519
7,943,778	B2	5/2011	Jiang et al.	
8,034,955	B2	10/2011	Gribble et al.	
8,067,394	B2	11/2011	Honda et al.	
8,067,465	B2	11/2011	Honda et al.	
8,071,632	B2	12/2011	Jiang et al.	514/364
8,088,824	B2	1/2012	Walling et al.	
8,124,656	B2	2/2012	Anderson et al.	514/660
8,124,799	B2	2/2012	Anderson et al.	552/284
8,129,429	B2	3/2012	Sporn et al.	514/510
8,258,329	B2	9/2012	Anderson et al.	
8,299,046	B2	10/2012	Sporn et al.	
8,309,601	B2	11/2012	Walling et al.	
8,314,137	B2	11/2012	Honda et al.	
8,338,618	B2	12/2012	Jiang et al.	
8,394,967	B2	3/2013	Jiang et al.	
8,440,820	B2	5/2013	Anderson et al.	
8,440,854	B2	5/2013	Anderson et al.	
8,455,544	B2	6/2013	Sporn et al.	
2002/0042535	A1	4/2002	Gribble et al.	
2003/0232786	A1	12/2003	Honda et al.	
2003/0236303	A1	12/2003	Gribble et al.	
2004/0002463	A1	1/2004	Honda et al.	
2004/0097436	A1	5/2004	Krasutsky et al.	514/169
2005/0159357	A1	7/2005	Hurez et al.	
2005/0208151	A1	9/2005	Hurez et al.	
2005/0276836	A1	12/2005	Wilson et al.	424/434
2005/0288363	A1	12/2005	Gribble et al.	558/303
2006/0258752	A1	11/2006	Vander Jagt et al.	
2007/0155742	A1	7/2007	Honda et al.	514/519
2007/0232577	A1	10/2007	Xu et al.	514/170
2007/0244081	A1	10/2007	Krasutsky et al.	514/169
2007/0249561	A1	10/2007	Taylor	514/365
2007/0259839	A1	11/2007	Krasutsky et al.	514/169
2007/0259842	A1	11/2007	Krasutsky et al.	514/169
2008/0220057	A1	9/2008	Gribble et al.	514/522
2008/0233195	A1	9/2008	Sporn et al.	514/63
2008/0261985	A1	10/2008	Honda et al.	548/400
2009/0048205	A1	2/2009	Meyer et al.	514/49
2009/0060873	A1	3/2009	Sporn et al.	424/85.6
2009/0093447	A1	4/2009	Konopleva et al.	514/510
2009/0326063	A1	12/2009	Sporn et al.	
2010/0041904	A1	2/2010	Jiang et al.	549/456
2010/0048887	A1	2/2010	Anderson et al.	540/8
2010/0048892	A1	2/2010	Anderson et al.	544/154
2010/0048911	A1	2/2010	Jiang et al.	548/250
2010/0056777	A1	3/2010	Anderson et al.	540/520
2010/0261930	A1	10/2010	Honda et al.	
2011/0009363	A1	1/2011	Honda et al.	
2011/0196007	A1	8/2011	Honda et al.	
2011/0245206	A1	10/2011	Jiang et al.	
2011/0245233	A1	10/2011	Anderson et al.	
2011/0281955	A1	11/2011	Meyer et al.	
2012/0071684	A1	3/2012	Walling et al.	
2012/0101149	A1	4/2012	Honda et al.	
2012/0214814	A1	8/2012	Anderson et al.	
2012/0220652	A1	8/2012	Sporn et al.	
2012/0238767	A1	9/2012	Jiang et al.	
2012/0245374	A1	9/2012	Anderson et al.	
2012/0283450	A1	11/2012	Anderson et al.	

DE	10 2005 041613	3/2007
EP	0 272 891 A2	6/1988
EP	0 329 348 B1	7/1995
EP	0 376 518 B1	11/1995
EP	0 576 230 B1	4/1996
EP	0 577 303 B1	10/1997
EP	0 712 860 B1	12/2001
GB	2 411 253 A	8/2005
JP	55-055153	4/1980
JP	2001 240573	9/2001
JP	2005-314381	11/2005
JP	2006 248909 A	9/2006
JP	2008-110962	5/2008
JP	2008-247898	10/2008
WO	WO 91/15498	10/1991
WO	WO 98/00173	1/1998
WO	WO 98/32762	7/1998
WO	WO 99/33483	7/1999
WO	WO 99/65478	12/1999
WO	WO 00/73253	12/2000
WO	WO 01/01135	1/2001
WO	WO 02/03996	1/2002
WO	WO 02/26761	4/2002
WO	WO 02/26762	4/2002
WO	WO 02/32410	4/2002
WO	WO-02/32410	4/2002
WO	WO 02/47611	6/2002
WO	WO-02/092768	11/2002
WO	WO 03/043631	5/2003
WO	WO 03/059339	7/2003
WO	WO 03/062260	7/2003
WO	WO 2004/064723	8/2004
WO	WO 2004/089357	10/2004
WO	WO 2004/105517	12/2004
WO	WO 2005/020932	3/2005
WO	WO 2005/042002	5/2005
WO	WO 2005/046732	5/2005
WO	WO-2005/063295	7/2005
WO	WO 2006/029221	3/2006
WO	WO 2006/102097	9/2006
WO	WO 2007/005879	1/2007
WO	WO 2007/069895	6/2007
WO	WO 2007/112043	10/2007
WO	WO-2007/127791	11/2007
WO	WO 2008/000068	1/2008
WO	WO 2008/000070	1/2008
WO	WO 2008/016095	2/2008
WO	WO-2008/063318	5/2008
WO	WO-2008/064132	5/2008
WO	WO-2008/064133	5/2008
WO	WO-2008/097596	8/2008
WO	WO 2008/111497	9/2008
WO	WO 2008/136838	11/2008
WO	WO 2009/023232	2/2009
WO	WO-2009/023845	2/2009
WO	WO-2009/058849	5/2009
WO	WO-2009/089545	7/2009
WO	WO 2009/129545	10/2009
WO	WO 2009/129546	10/2009
WO	WO 2009/129548	10/2009
WO	WO 2009/146216	12/2009
WO	WO 2009/146218	12/2009
WO	WO-2010/011782	1/2010
WO	WO-2010/053817	5/2010
WO	WO 2010/093944	8/2010
WO	WO-2011/130302	10/2011
WO	WO-2011/140078	11/2011
WO	WO-2012/106190	8/2012
WO	WO 2012/125488	9/2012

OTHER PUBLICATIONS

Andresen et al., "Preparation of dialkyl 2-cyanocycloalk-2-en-1-ones", *Journal of Chem. Res., Synopses*, (8), p. 332, 1994.*
 Woerdenbag et al., "Composition of the essential oils of *Kaempferia rotunda* L. and *Kaempferia angustifolia* Roscoe rhizomes from Indonesia." *Flavour and Fragrance Journal*, vol. 19, pp. 145-148, 2004.*

(56)

References Cited

OTHER PUBLICATIONS

- "CDDO in treating patients with metastatic or unresectable solid tumors or lymphoma," <http://www.clinicaltrials.gov/ct2/show/NCT00352040?term=CDDO&rank=1>, Dec. 14, 2008.
- "FDA mulls drug to slow late-stage Alzheimer's," <http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>, Retrieved on Sep. 23, 2003.
- "Phase IIa trial to determine the effects of bardoxolone methyl on renal function in patients with diabetic nephropathy," <http://www.clinicaltrials.gov/ct2/show/NCT00664027?term=rt&rank=10>, Dec. 14, 2008.
- "RTA 402 in advanced solid tumors or lymphoid malignancies," http://www.clinicaltrials.gov/ct2/show/NCT00508807?term=rt&rank=2&show_desc=Y, Dec. 14, 2008.
- "Study to assess the safety, tolerability, and pharmacodynamics of RTA 402 in patients with hepatic dysfunction," <http://www.clinicaltrials.gov/ct2/show/NCT00550849?term=rt&rank=4>, Dec. 14, 2008.
- Abad et al., "Diastereoselective synthesis of antiquorin and related polyoxygenated atisene-type diterpenes," *Tetrahedron*, 63 (7): 1664-1679, 2007.
- Abraham and Kappas, "Heme oxygenase and the cardiovascular-renal system," *Free Radic. Biol. Med.*, 39 (1): 1-25, 2005.
- Agarwal and Mehta, "Possible involvement of Bcl-2 pathway in resinoid X receptor alpha-induced apoptosis of HL-60 cells," *Biochem Biophys Res Commun.*, 230(2):251-253, 1997.
- Ahmad et al., "Triterpenoid CDDO-Me blocks the NF- κ B pathway by direct inhibition of IKK β on Cys-179," *J. Biol. Chem.*, 281: 35764-9, 2006.
- Akisanya et al., "West african timbers. XII. The interrelation of gedunin and khivorin," *J. Chem. Soc. Org.*, 5: 506-509, 1966.
- Akrivakis et al., "Prolonged infusion of gemcitabine in stage IV breast cancer: a phase I study," *Anti-Cancer Drugs*, 10 (6): 525-531, 1999.
- Al-almi et al., "Divergent effect of taxol on proliferation, apoptosis and nitric oxide production in MHH225 CD34 positive and U937 CD34 negative human leukemia cells," *Leukemia Res.*, 22:939-945, 1998.
- Alexander et al., "Synthesis and cytotoxic activity of two novel 1-dodecylthio-2-decyloxypropyl-3-phosphatidic acid conjugates with gemcitabine and cytosine arabinoside," *J. Med. Chem.*, 46 (19): 4205-4208, 2003.
- Ambis et al., "p53 and vascular endothelial growth factor regulate tumor growth of NOS2-expressing human carcinoma cells," *Nat. Med.*, 4(12):1371-1376, 1998.
- Amstutz et al., "Die position 5 im oxotremorin-gerüst: eine zentrale stelle für die steuerung der aktivität am muscarinischen rezeptor," *Helv. Chim. Acta.*, 70:2232-2244, 1987.
- Andreeff et al., "Expression of bcl-2-related genes in normal and AML progenitors: Changes induced by chemotherapy and cationic acid," *Leukemia*, 13:1881-1892, 1999.
- Andreeff et al., "PPARgamma nuclear receptor as a novel molecular target in leukemias," 2002 *Keystone Symposia*, Abstract No. 501, 2002.
- Andreeff, "Acute myeloid leukemia," In: *Cancer Treatment*, Haskell (Ed.), W. B. Saunders, 911-922, 1995.
- Anjaneyulu et al., "ent-Kaurane and beyerane diterpenoids from *Excoecaria agallocha*," *J. of Natural Products*, 65 (3): 382-385, 2002.
- Appendino et al., "Polycyclic diterpenoids from *Euphorbia characias*," *Fitoterapia*, 71 (2): 134-142, 2000.
- Araujo et al., "Systemic rather than local heme oxygenase-1 overexpression improves cardiac allograft outcomes in a new transgenic mouse," *J. Immunol.*, 171 (3): 1572-1580, 2003.
- Ardestani et al., "Effects of dexamethasone and betamethasone as COX-2 gene expression inhibitors on rigidity in a rat model of Parkinson's disease," *Indian J. Pharmacol.*, 39:235-9, 2007.
- Ariga et al., "Role of sphingolipid-mediated cell death in neurodegenerative diseases," *Journal of Lipid Research*, 39:1-16, 1998.
- Awale et al., "Four highly oxygenated isopimarane-type diterpenes of *Orthosiphon stamineus*," *Planta Medica*, 68 (3): 286-288, 2002.
- Awale et al., "Inhibition of NO production by highly-oxygenated diterpenes of orthosiphon stamineus and their structure-activity relationship," *Biological and Pharmaceutical Bulletin*, 26 (4): 468-473, 2003.
- Awale et al., "Norstaminane- and isopimarane-type diterpenes of *Orthosiphon stamineus* from Okinawa," *Tetrahedron*, 58 (27): 5503-5512, 2002.
- Baarschers et al., "The structure of some diterpenes from tambooti wood, *Spirostachys africana* sond," *J. of the Chemical Society*, 4046-4055, 1962.
- Bach, "Heme oxygenase-1 and transplantation tolerance," *Hum. Immunol.*, 67 (6): 430-432, 2006.
- Baeuerle, "NF- κ B: ten years after," *Cell*, 87:13-20, 1996.
- Bagasra et al., "Activation of the inducible form of nitric oxide synthase in the brains of patients with multiple sclerosis," *Proc. Natl. Acad. Sci. USA*, 92:12041-12045, 1995.
- Baker et al., "2'-Deoxy-2'-methylenecytidine and 2'-deoxy-2',2'-difluorocytidine 5'-diphosphates: potent mechanism-based inhibitors of ribonucleotide reductase," *J. Med. Chem.*, 34 (6): 1884, 1991.
- Baldwin, Jr., "The NF- κ B and I κ B proteins: new discoveries and insights," *Annu. Rev. Immunol.*, 14:649-681, 1996.
- Balkwill et al., "Smoldering and polarized inflammation in the initiation and promotion of malignant disease," *Cancer Cell*, 7 (3): 211-217, 2005.
- Bargou et al., "Constitutive nuclear factor κ B-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells," *J. Clin. Invest.*, 100:2961-2969, 1997.
- Barkett and Gilmore, "Control of apoptosis by Rel/NF- κ B transcription factors," *Oncogene*, 18:6910-6924, 1999.
- Barnes and Karin, "Nuclear factor- κ B—a pivotal transcription factor in chronic inflammation diseases," *N. Engl. J. Med.*, 336:1066-1071, 1997.
- Barrero et al., "Ring A functionalization of terpenoids by the unusual Baeyer-Villiger rearrangement of aliphatic aldehydes," *Synlett*, 6: 713-716, 1999.
- Barton et al., "Dehydrogenation of steroidal and triterpenoid ketones using benzeneseleninic anhydride," *J. Chem. Soc. Perkin Trans. 1.*, 2209, 1980.
- Beal, "Mitochondria, free radicals, and neurodegeneration," *Curr. Opin. Neurobiol.*, 6:661-666, 1996.
- Beran et al., "Topotecan and cytarabine is an active combination regimen in myelodysplastic syndromes and chronic myelomonocytic leukemia," *J. Clinical Oncology*, 17(9):2819-2830, 1999.
- Berge et al., "Addition of vinylketenes to enamines. A method for the preparation of 6,6-dialkylcyclohexa-2,4-dienones and 4,4-dialkyl-2-vinylcyclobutenones," *Helvetica Chimica Acta*, 65 (7): 2230-2341, 1982.
- Blard et al., "Glycosylation of acids under phase transfer conditions. Partial synthesis of saponins," *Tetrahedron Lett.*, 35:6107-6108, 1994.
- Bogdan and Ding, "Taxol, a microtubule-stabilizing antineoplastic agent, induces expression of tumor necrosis factor α and interleukin-1 in macrophages," *J. Leukoc. Biol.*, 52(1):119-121, 1992.
- Bogdan et al., "Contrasting mechanisms for suppression of macrophage cytokine release by transforming growth factor-beta and interleukin-10," *J. Biol. Chem.*, 267:23301-23308, 1992.
- Bollag and Holdener, "Retinoids in cancer prevention and therapy," *Annals of Oncology*, 3:513-526, 1992.
- Boolbol et al., "Cyclooxygenase-2 overexpression and tumor formation are blocked by sulindac in a murine model of familial adenomatous polyposis," *Cancer Res.*, 56(11):2556-2560, 1996.
- Bore et al., "The anti-inflammatory triterpenoid methyl 2-cyano-3,12-dioxoolean 1,9(11)-dien-28-oate methanol solvate hydrate," *Acta Crystallorg C.*, 58(Pt 3):o199-o200, 2002.
- Brookes et al., "The triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid and its derivatives elicit human lymphoid cell apoptosis through a novel pathway involving the unregulated mitochondrial permeability transition pore," *Cancer Res.*, 67:1793-1802, 2007.

(56)

References Cited

OTHER PUBLICATIONS

- Bruder and Caplan, "First bone formation and the dissection of an osteogenic lineage in the embryonic chick tibia is revealed by monoclonal antibodies against osteoblasts," *Bone*, 10:359-375, 1989.
- Bruder and Caplan, "A monoclonal antibody against the surface of osteoblasts recognizes alkaline phosphatase isoenzymes in bone, liver, kidney, and intestine," *Bone*, 11:189-198, 1990.
- Bruder et al., "Terminal Osteogenic cell differentiation in culture requires beta-glycerol phosphate," *Trans. Ortho. Res. Soc.*, 16:58, 1991.
- Bruland et al., "Expression and characteristics of a novel human osteosarcoma-associated cell surface antigen," *Cancer Res.*, 48:5302-5308, 1988.
- Buzoni-Gatel et al., "Intraepithelial lymphocytes traffic to the intestine and enhance resistance to *Toxoplasma gondii* oral infection," *J. Immunol.*, 162:5846-5852, 1999.
- Buzoni-Gatel et al., "Murine ileitis after intracellular parasite infection is controlled by TGF-beta-producing intraepithelial lymphocytes," *Gastroenterology*, 120:914-924, 2001.
- Cai and Vasella, "A new protecting group for alkynes: orthogonally protected dialkynes," *Helv. Chim. Acta.*, 78:732-757, 1995.
- Cambie et al., "Chemistry of the podocarpaceae. LXXVI, 8,13-Epoxy-3- β -hydroxylabda-14-en-2-one and 8,13-Epoxy-2-hydroxylabda-1,14-dien-3-one, new diterpenoids from *Lagarostrobos colensoi*," *Australian Journal of Chemistry*, 43 (4): 791-794, 1990.
- Campbell and Cromwell, "Endocyclic α,β -Unsaturated Ketones. VI. I Ultraviolet and Infrared Absorption Spectra and Resonance Stabilizations," *J. Am. Chem. Soc.*, 79:3456-3463, 1957.
- Cao et al., "Total synthesis of (-)-elegansidiol by using an abnormal Beckmann fragmentation of Hajos ketone oxime as a key step," *Tetrahedron*, 63 (23): 5036-5041, 2007.
- Carter et al., "Expression of survivin, a member of the inhibitor of apoptosis (IAP) family of caspase inhibitors is expressed in AML and regulated by cytokines and ATRA," *Blood*, 94(Suppl 1):479a, Abstract # 2142, 1999.
- Cassady and Suffness, In *Anticancer Agents Based on Natural Product Models*; Academic Press, NY, 254-269, 1980.
- Castaigne et al., "All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia," *Blood*, 76(9):1704-1709, 1990.
- Cerwenka and Swain, "TGF- β 1: immunosuppressant and viability factor for T lymphocytes," *Microbes and Infection*, 1: 1291-1296, 1999.
- Chaudhry et al., "The chemistry of the triterpenes and related compounds. Part XXXIX. Some derivatives of 4,4-dimethylcholestan-3-one," *J. of the Chemical Society*, 2725-2732, 1961.
- Chauhan et al., "The bortezomib/ proteasome inhibitor PS-341 and triterpenoid CDDO-Im induce synergistic anti-multiple myeloma (MM) activity and overcome bortezomib resistance," *Blood*, 103:3158-3166, 2004.
- Chen et al., "Chondrogenesis in chick limb bud mesodermal cells: reciprocal modulation by activin and inhibin," *Exp. Cell. Res.*, 206:119-27, 1993.
- Chen et al., "Stimulation of chondrogenesis in limb bud mesoderm cells by recombinant human bone morphogenetic protein 2B (BMP-2B) and modulation by transforming growth factor beta 1 and beta 2," *Exp. Cell. Res.*, 195:509-15, 1991.
- Cheng et al., "Differentiation of human bone marrow osteogenic stromal cells in vitro: induction of the osteoblast phenotype by dexamethasone," *Endocrinology*, 134:277-86, 1994.
- Chintharlapalli et al., "2-Cyano-3,12-dioxoolean-1,9-dien-28-oic acid and related compounds inhibit growth of colon cancer cells through peroxisome proliferator-activated receptor gamma-dependent and -independent pathways," *Mol. Pharmacol.*, 68:119-128, 2005.
- Chintharlapalli et al., "2-Cyano-lup-1-en-3-oxo-20-oic acid, a cyano derivative of betulonic acid, activates peroxisome proliferator-activated receptor [gamma] in colon and pancreatic cancer cells," *Carcinogenesis*, 28 (11): 2337-2346, 2007.
- Chintharlapalli et al., "Structure-dependent activity of glycyrrhetic acid derivatives as peroxisome proliferator-activated receptor [gamma] agonists in colon cancer cells," *Molecular Cancer Therapeutics*, 6 (5): 1588-1598, 2007.
- Cho et al., "The transcription factor NRF2 protects against pulmonary fibrosis," *FASEB Journal*, 18:1-29, 2004.
- Chou et al., "Stereospecific Synthesis of 2-Deoxy-2,2-difluororibonolactone and its Use in the Preparation of 2'-Deoxy-2', 2'-difluoro-B-D-ribofuranosyl Pyrimidine Nucleosides: The Key Role of Selective Crystallization," *Synthesis*, 565-570, 1992.
- Chow and Erdtman, "The chemistry of the natural order cupressales. 43. The structure and configuration of hinokiol and hinokione," *Acta Chemica Scandinavica*, 16: 1296-1300, 1962.
- Chung and Wasicak, "Synthesis of chiral ∇ -acetylenic cyclic amines from ∇ -amino acids: App.s to differentially constrained oxotremorine analogues as muscarinic agents," *Tetrahedron Lett.*, 31:3957-3960, 1990.
- Cianchi et al., "Cyclooxygenase-2 activation mediates the proangiogenic effect of nitric oxide in colorectal cancer," *Clinical Cancer Research*, 10:2694-2704, 2004.
- Clinton et al., "Steroidal[3,2-c]pyrazoles. II. Androstanes, 19-norandrostanes and their unsaturated analogs," *J. Am. Chem. Soc.*, 83:1478-1491, 1961.
- Corey and Ruden, "Stereoselective methods for the synthesis of terminal *cis* and *trans* enyne units," *Tetrahedron Lett.*, 1495-1499, 1973.
- Coyle and Puttfarcken, "Oxidative stress, glutamate, and neurodegenerative disorders," *Science*, 262:689-695, 1993.
- Crespi-Perellino et al., "Identification of new diterpenoids from *Euphoria calyptrata* cell cultures," *J. of Natural Products*, 59 (8): 773-776, 1996.
- Cripe, "Adult Acute Leukemia," *Current Problems in Cancer*, 21 (1): 4-64, 1997.
- Cromwell et al., "Endocyclic α,β -unsaturated ketones. V. ¹ Synthesis and reaction of 3-bromo-1,1-dimethyl-2-keto-1,2-dihydronaphthalene with morpholine," *J. of Organic Chemistry*, 22: 520-523, 1957.
- Cui, "A material science perspective of pharmaceutical solids," *Int. J. Pharmaceutics*, 339 (1-2): 3-18, 2007.
- Danishefsky et al., "Diels-Alder reactions of *trans*-1-methoxy-3-trimethylsilyloxy-1, 3-butadiene," *J. Am. Chem. Soc.*, 101: 6996-7000, 1979.
- De Mico et al., "A Versatile and Highly Selective Hypervalent Iodine (III)/2,2,6,6-Tetramethyl-1-piperidinyloxy-Mediated Oxidation of Alcohols to Carbonyl Compounds," *J. Org. Chem.*, 62: 6974, 1997.
- De Ruggieri et al., "Deidrogenazione e bromurazione di beta-chetonitrili steroidal," *Il Farmaco*, 20: 358-388, 1964. (English summary).
- Dean et al., "Halogenolysis of methyl glycyrrhetate with lithium iododimethylformamide," *J. Chem. Soc.*, 6655-6659, 1965.
- Deng and Snyder, "Preparation of a 24-Nor-1,4-dien-3-one triterpene derivative from betulin: a new route to 24-nortriterpene analogues," *J. of Organic Chemistry*, 67 (9): 2864-2873, 2002.
- Dezube et al., "Interim results of a phase I trial with a novel orally administered synthetic triterpenoid RTA 402 (CDDO-Me) in patients with solid tumors and lymphoid malignancies," *J. Clin. Oncol.*, 2007 ASCO Annual Meeting Proceedings, 25(18S):14101, 2007.
- Di Stefano et al., "Inhibition of [3H]thymidine incorporation into DNA of rat regenerating liver by 2',2'-difluorodeoxycytidine coupled to lactosaminated poly-L-lysine," *Biochem. Pharmacol.*, 57 (7): 793-799, 1999.
- Ding et al., "Macrophage deactivating factor and transforming growth factors- β 1, β 2 and β 3, inhibit induction of macrophage nitrogen oxide synthesis by IFN γ ," *J. Immunol.*, 145:940-944, 1990.
- Dinkova-Kostova et al., "Extremely potent triterpenoid inducers of the phase 2 response: correlations of protection against oxidant and inflammatory stress," *PNAS*, 102:4584-4589, 2005.
- Drach et al., "Induction of differentiation in myeloid leukemia cell lines and acute promyelocytic leukemia cells by liposomal all-trans-retinoic acid," *Cancer Research*, 53:2100-2104, 1993.
- Dragnev et al., "Specific chemopreventive agents trigger proteasomal degradation of G1 cyclins: implications for combination therapy," *Clin. Cancer Research*, 10 (7): 2570-2577, 2004.

(56)

References Cited

OTHER PUBLICATIONS

- Dragnev et al., "The retinoids and cancer prevention mechanisms," *The Oncologist*, 5:361-368, 2000.
- Drefahl and Huneck, "Nor-olea-12-enol-17-amin und Olea-12-enol-28-amin," *Chem. Ber.*, 91:278-281, 1958.
- Duan et al., "Immunosuppressive terpenoids from extracts of *Tripterygium wilfordii*," *Tetrahedron*, 57 (40): 8413-8424, 2001.
- DuBois et al., "G₁ delay in cells overexpressing prostaglandin endoperoxide synthase-2¹," *Cancer Res.*, 56(4):733-737, 1996.
- DuBois et al., "Increased cyclooxygenase-2 levels in carcinogen-induced rat colonic tumors," *Gastroenterology*, 110:1259-1262, 1996.
- Dutcher et al., "Pentacyclic triterpene synthesis. 5. Synthesis of optically pure ring AB precursors," *J. Org. Chem.*, 41:2663-2669, 1976.
- Eistert et al., "Reaktionen von diazoalkanen mit α -diketonen und chinonen, XII. ringerweiterung von 1.1-dimethyl-indandion-(2.3)," *Chemische Berichte*, 102 (7): 2429-2439, 1969.
- Ekmekcioglu et al., "Tumor iNOS predicts poor survival for stage III melanoma patients," *Int. J. Cancer*, 119:861-866, 2006.
- Ekong and Olagbemi, "West African timbers. Part XVII. Correlation of gedunin, methyl angolensate, and andirobin," *J. of the Chemical Society, [Section] C: Organic*, 10: 944-966, 1966.
- Ellies et al., "Mammary tumor latency is increased in mice lacking the inducible nitric oxide synthase," *Int. J. Cancer*, 106:1-7, 2003.
- Elliot et al., "The triterpenoid CDDO inhibits expression of matrix metalloproteinase-1, matrix metalloproteinase-13 and Bcl-3 in primary human chondrocytes," *Arthritis Res. Ther.*, 5:R285-R291, 2003.
- Elsawa et al., "Preferential Inhibition of Malignant Cell Growth by CDDO in Waldenstrom Macroglobulinemia," *Blood*, 108(11):2528, 2006.
- Elstner et al., "Ligands for peroxisome proliferator-activated receptor γ and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells in vitro and in BNX mice," *Proc. Natl. Acad. Sci. USA*, 95:8806-8811, 1998.
- Embleton et al., "Antitumour reactions of monoclonal antibody against a human osteogenic-sarcoma cell line," *Br. J. Cancer*, 43:4801-4805, 1981.
- Engel et al., "Quantitation of minimal residual disease in acute myelogenous leukemia and myelodysplastic syndromes in complete remission by molecular cytogenetics of progenitor cells," *Leukemia*, 13:568-577, 1999.
- English translation of office communication issued in Eurasian patent application 201001556/28, dated Apr. 27, 2012.
- Estey et al., "Molecular remissions induced by liposomal-encapsulated all-trans retinoic acid in newly diagnosed acute promyelocytic leukemia," *Blood*, 94:2230-2235, 1999.
- Estey et al., "Randomized phase II study of fludarabine + cytosine arabinoside + idarubicin + all-trans retinoic acid + granulocyte-colony stimulating factor in poor prognosis newly diagnosed acute myeloid leukemia and myelodysplastic syndrom," *Blood*, 93(8):2478-2484, 1999.
- Favaloro, Jr. et al., "Design and synthesis of tricyclic compounds with enone functionalities in rings A and C: a novel class of highly active inhibitors of nitric oxide production in mouse macrophages," *J Med Chem*, 45(22):4801-4805, 2002.
- Ferreira et al., "Phytochemistry of the mopane, *Colophospermum mopane*," *Phytochemistry*, 64 (1): 31-51, 2003.
- Finkbeiner and Stiles, "Chelation as a driving force in organic reactions. IV. Synthesis of a ∇ -nitro acids by control of the carboxylation-decarboxylation equilibrium," *J. Am. Chem. Soc.*, 85:616-622, 1963.
- Fraga et al., "Partial synthesis of a colensenone isomer," *Anales de Quimica*, 90 (7-8): 513-516, 1994.
- Gandhi et al., "Prolonged infusion of gemcitabine: clinical and pharmacodynamic studies during a phase I trial in relapsed acute myelogenous leukemia," *J. Clin. Oncol.*, 20 (3): 665-673, 2002.
- Genain and Hauser, "Creation of a model for multiple sclerosis in *Callithrix jacchus* marmosets," *J. Mol. Med.*, 75:187-197, 1997.
- Ghosh et al., "NF- κ B and Rel proteins: evolutionarily conserved mediators of immune response," *Annu Rev Immunol.*, 16:225-260, 1998.
- Godoy et al., "Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease," *Brain*, 131:1880-1894, 2008.
- Granger et al., "Stereospecificity in 2,3-diethylindanone syntheses. II. Synthesis 2-ethyl-5-hydroxy (or 5-methoxy)-3-methylindanones," *Bulletin de la Societe Chimique de France*, 815-819, 1957.
- Grant and Carman, "Colensenone," *J. of the Chemical Society*, 3740-3746, 1962.
- Grant et al., "Boron trifluoride catalyzed rearrangements of novel epoxide derivatives of manool and manoyl oxide," *Australian Journal of Chemistry*, 46 (8): 1125-1145, 1993.
- Grieco and Speake, "Synthetic Studies on Quassinoids: Total Synthesis and Biological Evaluation of (+)-Des-D-chaparrinone," *J. Org. Chem.*, 63:5929-5936, 1998.
- Guo et al., "Selective Protection of 2',2'-Difluoro deoxycytidine (Gemcitabine)," *J. Org. Chem.*, 64: 8319-8322, 1999.
- Guo et al., "Targeted delivery of a peripheral benzodiazepine receptor ligand-gemcitabine conjugate to brain tumors in a xenograft model," *Cancer Chemother. Pharmacol.*, 48 (2): 169-176, 2001.
- Gura et al., "Systems for identifying new drugs are often faulty," *Science*, 278:1041-1042, 1997.
- Guttridge et al., "NF- κ B controls cell growth and differentiation through transcriptional regulation of cyclin D1," *Mol. Cell. Biol.*, 19 (8): 5785-5799, 1999.
- Hail et al., "Evidence supporting a role for calcium in apoptosis induction by the synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO)," *J. Biol. Chem.*, 279:11179-11187, 2004.
- Hanson and White, "The chemistry of the tetracyclic diterpenoids—XV: The complete structure of abbeokutone," *Tetrahedron*, 26 (20): 4839-4841, 1970.
- Hatcher et al., "Curcumin: from ancient medicine to current clinical trials," *CMLS Cellular and Molecular Life Sciences*, 65 (11): 1631-1652, 2008.
- Heiner et al., "Localization of GD2-specific monoclonal antibody 3F8 in human osteosarcoma," *Cancer Res.*, 47:5377-5384, 1987.
- Hemmert et al., "Nuclear magnetic response. II. Methyl groups of lanostane," *Bulletin de la Societe Chimique de France*, 3: 976-982, 1966.
- Hemmert et al., "Nuclear magnetic response. III. Methyl groups of 4,4-dimethylcholestan," *Bulletin de la Societe Chimique de France*, 3: 982-987, 1966.
- Herzon and Meyers, "Enantioselective Synthesis of Stephacidin B," *J. of the American Chemical Society*, 127 (15): 5342-5344, 2005.
- Hidvegi et al., "A low temperature method of isolating normal human articular chondrocytes," *Osteoarthritis Cartil.*, 14:89-93, 2006.
- Hill et al., "Synthetical approaches to the pristimerin chromophore," *J. of the Chemical Society*, 361-375, 1965.
- Hinz et al., "NF- κ B function in growth control: regulation of cyclin D1 expression and G0/G1-to-S-phase transition," *Mol. Cell. Biol.*, 19 (4): 2690-2698, 1999.
- Hirota et al., "Stereoselective total synthesis of (\pm)-eperuane-8 β ,15-diol," *Bull. Chem. Soc. Jpn.*, 61:4023-4028, 1988.
- Hirota et al., "Total synthesis of (\pm)-amarolide, a quassinoid bitter principle," *J Org. Chem.*, 56:1119-1127, 1991.
- Hirota et al., "Suppression of tumor promoter-induced inflammation of mouse ear by ursolic acid and 4,4-dimethylcholestan derivatives" *Agric. Biol. Chem.*, 54:1073-1075, 1990.
- Honda et al., "A novel dicyanotriterpenoid, 2-cyano-3,12-dioxooleanan-1,9(11)-dien-28-onitrile, active at picomolar concentrations for inhibition of nitric oxide production," *Bioorganic & Medicinal Chemistry Letters*, 12:1027-1030, 2002.
- Honda et al., "An efficient synthesis of tricyclic compounds (\pm)-(4a β , 8a β , 10a α)-1,2,3,4,4a,6,7,8,8a,9,1-,10a-Dodecahydro-1,1,4a-Trimethyl-2-Oxophenanthrene-8a-Carboxylic acid, its methyl ester, and (\pm)-(4a β , 8a β , 10a α)-3,4,4a,6,7,8,8a,9,10,10a-Decahydro-8a-Hydroxymethyl-1,1,4a-Trimethylphenanthren-2(1H)-one," *Org. Prep. Proced. Int.*, 37 (6):546-550, 2005.

(56)

References Cited

OTHER PUBLICATIONS

- Honda et al., "Design and synthesis of 23,24-dinoroleanolic acid derivatives, novel triterpenoid-steroid hybrid molecules," *J. Org. Chem.*, 63:4846-4849, 1998.
- Honda et al., "Design and synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages," *Bioorg Med Chem Lett.*, 8(19):2711-2714, 1998.
- Honda et al., "Design, synthesis, and biological evaluation of biotin conjugates of 2-cyano-3,12-dioxoolean-1,9(11)-dien-28-oic acid for the isolation of the protein targets," *J. Med. Chem.*, 47 (20): 4923-4932, 2004.
- Honda et al., "Efficient synthesis of (-) and (+)-tricyclic compounds with enone functionalities in rings A and C. A novel class of orally active anti-inflammatory and cancer chemopreventive agents," *Org Biomol Chem.*, 1:4384-4391, 2003.
- Honda et al., "New enone derivatives of oleanolic acid and ursolic acid as inhibitors of nitric oxide production in mouse macrophages," *Bioorg. Med. Chem. Lett.*, 7:1623-1628, 1997.
- Honda et al., "Novel synthetic oleanane and ursane triterpenoids with various enone functionalities in ring A as inhibitors of nitric oxide production in mouse macrophages," *J Med. Chem.*, 43:1866-1877, 2000.
- Honda et al., "Novel synthetic oleanane triterpenoids: a series of highly active inhibitors of nitric oxide production in mouse macrophages," *Bioorg Med Chem Lett.*, 9(24):3429-3434, 1999.
- Honda et al., "Novel tricyclic compounds having acetylene groups at C-8a and cyano enones in rings A and C: highly potent anti-inflammatory and cytoprotective agents," *J Med. Chem.*, 50:1731-1734, 2007.
- Honda et al., "Revision and confirmation of the regiochemistry of isoxazoles derived from methyl oleanonate and lanost-8-en-3-one. Synthesis of a new lanostane triterpenoid with a cyano-enone functionality in ring A," *J Org. Chem.*, 68:4991-4993, 2003.
- Honda et al., "Synthesis of (\pm)-3,3-ethylenedioxy-14 α -hydroxy-5-picrasene-11,16-dione, a 14 α H-picrasane derivative," *Chem. Lett.*, 299-302, 1981.
- Honda et al., "Synthesis of a novel dicyano abietane analogue: a potential antiinflammatory agent," *J. Org. Chem.*, 71:3314-3316, 2006.
- Honda et al., "Synthetic oleanane and ursane triterpenoids with modified rings A and C: A series of highly active inhibitors of nitric oxide production in mouse macrophages," *J. Med. Chem.*, 43:4233-4246, 2000.
- Hong et al., "Phase I trial of a novel oral NF- κ B/pSTAT3 inhibitor RTA-402 in patients with solid tumors and lymphoid malignancies," 44th Annual Meeting of the American Society of Clinical Oncology, 2008.
- Hosoi et al., "Detection of human osteosarcoma-associated antigen(s) by monoclonal antibodies," *Cancer Res.*, 42:654-661, 1982.
- Huang et al., "Inhibition of skin tumorigenesis by Rosemary and its constituents carnosol and ursolic acid," *Cancer Res.*, 54:701-708, 1994.
- Huang et al., "Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice," *Cancer Res.*, 54:5841-5847, 1994.
- Huang et al., "Structure of a WW domain containing fragment of dystrophin in complex with β -dystroglycan," *Nat. Struct. Biol.*, 7:634-638, 2000.
- Hyer et al., "Synthetic triterpenoids cooperate with tumor necrosis factor-related apoptosis-inducing ligand to induce apoptosis of breast cancer cells," *Cancer Res.*, 65:4799-4808, 2005.
- Iddon et al., "Synthesis and reactions of 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-11-one (2,5-dimethyl-9-oxo-6,7-benzomorphan); a new route to 3-benzazocines," *J. of the Chemical Society, Perkin Transactions 1: Organic and bio-Organic Chemistry*, 10: 2583-2593, 1983.
- Iguchi et al., "Lipid peroxidation and disintegration of the cell membrane structure in cultures of rat lung fibroblasts treated with asbestos," *J. Appl. Toxicol.*, 13:269-275, 1993.
- Ikeda et al., "Induction of redox imbalance and apoptosis in multiple myeloma cells by the novel triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid," *Mol. Cancer Ther.*, 3:39-45, 2004.
- Ikeda et al., "The novel triterpenoid CDDO and its derivatives induce apoptosis by disruption of intracellular redox balance," *Cancer Res.*, 63:5551-5558, 2003.
- Ishikawa et al., "Heme oxygenase-1 inhibits atherogenesis in Watanabe heritable hyperlipidemic rabbits," *Circulation*, 104 (15): 1831-1836, 2001.
- Ito et al., "Involvement of caspase-8 in the induction of osteosarcoma cell apoptosis by the novel triterpenoid CDDO," 47th Annual Meeting, Orthopaedic Research Society, Feb. 25-28, 2001, San Francisco, California, p. 0863, Poster Session, 2001.
- Ito et al., "The novel triterpenoid 2-cyano-3, 12-dioxoolean-1,9-dien-28-oic acid induces apoptosis of human myeloid leukemia cells by a caspase-8-dependent mechanism," *Cell Growth & Differentiation*, 11(5):261-267, 2000.
- Ito et al., "The novel triterpenoid CDDO induces apoptosis and differentiation of human osteosarcoma cells by a caspase-8 dependent mechanism," *Mol. Pharmacol.*, 59:1094-1099, 2001.
- Johansen et al., "Pharmacology and preclinical pharmacokinetics of the triterpenoid CDDO methyl ester," *Proc. Amer. Assoc. Cancer Res.*, 44:1728, 2003.
- Johnson et al., "A plan for distinguishing between some five- and six-membered ring ketones," *J. Am Chem. Soc.*, 67:1745-1754, 1945.
- Johnson et al., "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials," *Br. J. Cancer*, 84:1424-1431, 2001.
- Joyce et al., "Integration of Rac-dependent regulation of cyclin D1 transcription through a nuclear factor-kappaB-dependent pathway," *J. Biol. Chem.*, 274 (236): 25245-25249, 1999.
- Kahne and Collum, "Kinetic cyanations of ketone enolates," *Tetrahedron Lett.*, 22:5011-5014, 1981.
- Kaltschmidt et al., "Transcription factor NF-kappaB is activated in primary neurons by amyloid beta peptides and in neurons surrounding early plaques from patients with Alzheimer disease," *Proc. Natl. Acad. Sci. USA*, 94:2642-2647, 1997.
- Karin, "Nuclear factor-kappaB in cancer development and progression," *Nature*, 441:431-436, 2006.
- Kasinski et al., "Inhibition of IkappaB kinase-nuclear factor-kappaB signaling pathway by 3,5-bis(2-fluorobenzylidene)piperidin-4-one (EF24), a novel monoketone analog of curcumin," *Mol. Pharmacology*, 74 (3): 654-661, 2008.
- Kawamori et al., "Chemopreventive activity of celecoxib, as specific cyclooxygenase-2 inhibitor, against colon carcinogenesis," *Cancer Res.*, 58(3):409-412, 1998.
- Kerwin et al., "Quassinoid synthesis. 2. Preparation of a tetracyclic intermediate having the Bruceantin tetrahydrofuran ring," *J. Org. Chem.*, 52:1686-1695, 1987.
- Khan et al., "A dichotomous role for nitric oxide during acute Toxoplasma gondii infection in mice," *Proc. Natl. Acad. Sci. USA*, 94:13955-13960, 1997.
- Kim et al., "Capase-3 activation is involved in apoptosis induced by a synthetic triterpenoid in Non-small cell lung cancer (NSCLC) cells," *Proc. Amer. Assoc. Cancer Res.*, 41:770, Abstract #4894, 2000.
- Kim et al., "Identification of a novel synthetic triterpenoid, methyl-2-cyano-3,12-dioxoolean-1,9-dien-28-oate, that potentially induces caspase-mediated apoptosis in human lung cancer cells," *Molecular Cancer Therapeutics*, 1:177-184, 2002.
- Kincl et al., "Pituitary gonadotropin inhibitory action of nentral steroids," *Acta. Endocrinologica*, 46: 300-306, 1964.
- Kircher, "Triterpenes, in organ pipe cactus," *Phytochemistry*, 19:2707-2712, 1980; Database CAPLUS on STN AN:1981:550946.
- Klotz et al., "Selective expression of inducible nitric oxide synthase in human prostate carcinoma," *Cancer*, 82:1897-1903, 1998.
- Kokpol et al., "Structure of trigonostemone, a new phenanthrenone from the thai plant *Trigonostemon reidioides*," *Journal of Natural Products*, 53 (5): 1148-1151, 1990.
- Konishi et al., "Anti-tumor-promoting activity of diterpenes from *Excoecaria agallocha*," *Biological and Pharmaceutical Bulletin*, 21 (9): 993-996, 1998.

(56)

References Cited

OTHER PUBLICATIONS

- Konishi et al., "Five new labdane-type diterpenes from *Excoecaria agallocha* IV," *Chemical and Pharmaceutical Bulletin*, 46 (9): 1393-1398, 1998.
- Konopleva and Andreeff, "Regulatory pathways in programmed cell death," *Cancer Mol Biol.*, 6:1229-1260, 1999.
- Konopleva et al., "Activation of nuclear transcription factor PPARgamma by the novel triterpenoid CDDO as targeted therapy in breast cancer," *2002 Keystone Symposium*, Abstract No. 539, 2002.
- Konopleva et al., "Apoptosis: molecules and mechanisms," *Adv Exp Med Biol*, 457:217-236, 1998.
- Konopleva et al., "Engraftment potential of AML progenitors into NOD/scid mice is dependent on baseline CXCR4 expression," *Blood*, 94(Suppl 1):166b, Abstract #3916, 1999.
- Konopleva et al., "Mechanisms and Activity of PPARgamma-Active Triterpenoids CDDO and CDDO-Me in Leukemias," *Blood*, 106:2460, 2005.
- Konopleva et al., "Novel synthetic triterpenoid CDDO-Me: potent antiproliferative, proapoptotic and differentiating agent in AML," *Blood*, 96(11), Part 1: 121A, abstract # 522, 2000.
- Konopleva et al., "Novel synthetic triterpenoid, CDDO, and its methyl ester: Potent antiproliferative, proapoptotic and differentiating agents in AML," *Blood*, 94(Suppl 1):479a, Abstract #2140, 1999.
- Konopleva et al., "Novel triterpenoid CDDO-Me is a potent inducer of apoptosis and differentiation in acute myelogenous leukemia," *Blood*, 99(1):326-335, 2002.
- Konopleva et al., "Peroxisome proliferator-activated receptor gamma and retinoid X receptor ligands are potent inducers of differentiation and apoptosis in leukemias," *Mol. Cancer Ther.*, 3:1249-1262, 2004.
- Konopleva et al., "PPAR γ nuclear receptor as a novel therapeutic target in AML," *Blood*, 96(11):460a, Abstract #1982, 2000.
- Konopleva et al., "PPARgamma Ligand CDDO Induces Apoptosis in Leukemias Via Multiple Apoptosis Pathways," *Abstracts of the 44th Annual Meeting of the American Society of Hematology*, Abstract No. 2209, 2002.
- Konopleva et al., "PPARgamma Ligands Are Potent Inducers of Apoptosis in Leukemias and Lymphomas," *American Society of Hematology 43rd Annual Meeting and Exposition*, Abstract No. 501, 2001.
- Konopleva et al., "PPARgamma Nuclear Receptor as a Novel Molecular Target in Leukemia Therapy," *Proc. Amer. Assoc. Cancer Res.*, 43:4730, 2002.
- Konopleva et al., "Suppression of ERK Activation is Required for Triterpenoid Methyl-CDDO-Induced Apoptosis in AML," *Blood*, 102(11):1404, 2003.
- Konopleva et al., "Synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid induces growth arrest in HER2-overexpressing breast cancer cells," *Mol. Cancer Ther.*, 5:317-328, 2006.
- Konopleva et al., "Synthetic triterpenoid CDDO as a novel therapy for resistant breast cancer," *Proc. Amer. Assoc. Cancer Res.*, 44:2726, 2003.
- Konopleva et al., "The novel triterpenoid CDDO-Me suppresses MAPK pathways and promotes p38 activation in acute myeloid leukemia cells," *Leukemia*, 19:1350-1354, 2005.
- Konopleva et al., "The synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid induces caspase-dependent and -independent apoptosis in acute myelogenous leukemia," *Cancer Res.*, 64:7927-7935, 2004.
- Konopleva et al., "Triterpenoid methyl-CDDO is a potent inducer of apoptosis in CD34+ AML progenitor cells via activation of SAPK pathways and inhibition of MAPK cascades," *Blood*, 104:2533, 2004.
- Kornblau et al., "Apoptosis regulating proteins as targets of therapy for hematological malignancies," *Exp. Opin. Inv. Drugs*, 8:2027-2057, 1999.
- Kornblau et al., "Phase I study of mitoxantrone plus etoposide with multidrug blockage by SDZ PSC-833 in relapsed or refractory acute myelogenous leukemia," *J. Clin. Oncol.*, 15(5):1796-1802, 1997.
- Korovin and Tkachev, "Synthesis of quinoxalines fused with triterpenes, ursolic acid and betulin derivatives," *Russian Chemical Bulletin*, (Translation of *Izvestiya Akademii Nauk, Seriya Khimicheskaya*), 20 (2): 304-310, 2001.
- Kowalski and Reddy, "Ester homologation revisited: a reliable, higher yielding and better understood procedure," *J. Org. Chem.*, 57:7194-7208, 1992.
- Kress et al., "Triterpenoids display single agent activity in a mouse model of CLL/SBL," *Blood*, 108(11):2530, 2006.
- Kress et al., "Triterpenoids display single agent anti-tumor activity in a transgenic mouse model of chronic lymphocytic leukemia and small B cell lymphoma," *PLOS ONE*, 6(e559):1-11, 2007.
- Kruger et al., "Up-regulation of heme oxygenase provides vascular protection in an animal model of diabetes through its antioxidant and antiapoptotic effects," *J. Pharmacol. Exp. Ther.*, 319 (3): 1144-1152, 2006.
- Kumar and Seshadri, "A new triterpene from *Pterocarpus santalinus* bark," *Phytochemistry*, 15 (9): 1417-1418, 1976.
- Kurbacher et al., "Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro," *Cancer Lett.*, 103:183-189, 1996.
- Kurinna et al., "The novel triterpenoid CDDO-Me promotes apoptosis in Gleevec-resistant chronic myeloid leukemia cells by caspase-independent mechanisms," *Proc. Amer. Assoc. Cancer Res.*, 46:2240, 2005.
- Laing et al., "The x-ray crystal and molecular structure of a tetracyclic diterpenoid-benzaldehyde reaction product and the long range protective influence of its benzene ring," *Tetrahedron Letters*, 32: 3043-3046, 1973.
- Lala et al., "Role of nitric oxide in tumor progression: lessons from experimental tumors," *Cancer and Metastasis Reviews*, 17 (1): 91-106, 1998.
- Langille et al., "Differential effects of physiological concentrations of retinoic acid in vitro on chondrogenesis and myogenesis in chick craniofacial mesenchyme," *Differentiation*, 40:84, 1989.
- Lapillonne et al., "Activation of peroxisome proliferator-activated receptor gamma by a novel synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid induces growth arrest and apoptosis in breast cancer cells," *Cancer Res.*, 63:5926-5939, 2003.
- Larock et al., "Carbocycle synthesis via carbopalladation of nitriles," *J. of the American Chemical Society*, 121 (13): 3238-3239, 1999.
- Lawson et al., "Isolation and preliminary characterization of a monoclonal antibody that interacts preferentially with the liver isoenzyme of human alkaline phosphatase," *Clin. Chem.*, 31:381-385, 1985.
- Lee et al., "Functional and quantitative analysis of splenic T cell immune responses following oral toxoplasma gondii infection in mice," *Experimental Parasitology*, 91:212-221, 1999.
- Lemieux, "Acylglycosyl Halides. [55] tetra-O-acetyl- α -D-glucopyranosyl bromide," *Methods Carbohydr. Chem.*, 2:221-222, 1963.
- Leonard et al., "Expression of nitric oxide synthase in inflammatory bowel disease is not affected by corticosteroid treatment," *J. Clin. Pathol.*, 51:750-753, 1998.
- Levy and Lavie, "Attempted skeletal rearrangements in the lanostane series," *Israel J. of Chemistry*, 8 (4): 677-684, 1970.
- Li and Nel, "Role of the Nrf2-mediated signaling pathway as a negative regulator of inflammation: implications for the impact of particulate pollutants on asthma," *Antioxidants & Redox Signaling*, 8:88-98, 2006.
- Liby et al., "A novel acetylenic tricyclic bis-(cyano enone) potentially induces phase 2 cytoprotective pathways and blocks liver carcinogenesis induced by aflatoxin," *Cancer Res.*, 68:6727-6733, 2008.
- Liby et al., "Novel semisynthetic analogues of betulinic acid with diverse cytoprotective, antiproliferative, and proapoptotic activities," *Molecular Cancer Therapeutics*, 6 (7): 2113-2119, 2007.
- Liby et al., "The rexinoid LG100268 and the synthetic triterpenoid CDDO-methyl amide are more potent than erlotinib for prevention of mouse lung carcinogenesis," *Mol. Cancer Ther.*, 7:1251-1257, 2008.
- Liby et al., "The synthetic triterpenoids, CDDO and CDDO-imidazolidine, are potent inducers of heme oxygenase-1 and Nrf2/ARE signaling," *Cancer Res.*, 65:4789-4798, 2005.

(56)

References Cited

OTHER PUBLICATIONS

- Liby et al., "Triterpenoids and rexinoids as multifunctional agents for the prevention and treatment of cancer," *Nature Reviews Cancer*, 7:357-369, 2007.
- Lieu et al., "Dual cytotoxic mechanisms of submicromolar taxol on human leukemia HL-60 cells," *Biochem. Pharmacology*, 53:1587-1596, 1997.
- Ling et al., "The novel triterpenoid C-28 methyl ester of 2-cyano-3, 12-dioxoolen-1, 9-dien-28-oic acid inhibits metastatic murine breast tumor growth through inactivation of STAT3 signaling," *Cancer Res.*, 67:4210-4218, 2007.
- Ling et al., "The novel triterpenoid CDDO-Me inhibits metastatic murine breast tumor through inhibition of Stat3 signaling," 2007 AACR Annual Meeting, Abstract No. 301, 2007.
- Liotta et al., "A simple method for the efficient synthesis of unsaturated Δ^3 -dicarbonyl compounds," *J. Org. Chem.*, 46:2920-2923, 1981.
- Liu et al., "Chemical constituents from root of *Rubus irenaeus*," *Zhongcaoyao*, 34 (5): 394-396, 2003.
- Liu et al., "Heme oxygenase-1 (HO-1) inhibits postmyocardial infarct remodeling and restores ventricular function," *FASEB J.*, 20 (2): 207-216, 2006.
- Long, "Regulation of human bone marrow-derived osteoprogenitor cells by osteogenic growth factors," *Clin. Invest.*, 95:881-887, 1995.
- Luo et al., "IKK/NF-kappaB signaling: balancing life and death—a new approach to cancer therapy," *J. Clin. Invest.*, 115 (10): 2625-2631, 2005.
- Ma et al., "Two pimarane diterpenoids from *Ephemerantha lonchophylla* and their evaluation as modulators of the multidrug resistance phenotype," *J. of Natural Products*, 61 (1): 112-115, 1998.
- MacMicking et al., "Altered responses to bacterial infection and endotoxic shock in mice lacking inducible nitric oxide synthase," *Cell*, 81:641-650, 1995.
- Mai et al., "Epigenetic multiple ligands: mixed histone/protein methyltransferase, acetyltransferase, and class III deacetylase (sirtuin) inhibitors," *J. Med. Chemistry*, 51 (7): 2008.
- Mantovani et al., "Inflammation by remote control," *Nature*, 435:752-753, 2005.
- Marnett, "Aspirin and the potential role of prostaglandins in colon cancer," *Cancer Res.*, 52(20):5575-5589, 1992.
- Marples and Spilling, "Ene reactions of unsaturated acyloins," *Tetrahedron Letters*, 26 (52): 6515-6518, 1985.
- Marples and Spilling, "Facile intramolecular ene reactions of steroidal unsaturated acyloins," *Tetrahedron*, 48 (19): 4017-4026, 1992.
- Marrogi et al., "Nitric oxide synthase, cyclooxygenase 2, and vascular endothelial growth factor in the angiogenesis of non-small cell lung carcinoma," *Clinical Cancer Research*, 6:4739-4744, 2000.
- Matsumoto et al., "Synthesis of pygmaecocine E, a linear abietane diterpene from *Pygmaeopremna herbacea* (Roxb.) moldenke," *Chemical and Pharmaceutical Bulletin*, 44 (7): 1318-1325, 1996.
- Maurel et al., "Phase I trial of weekly gemcitabine at 3-h infusion in refractory, heavily pretreated advanced solid tumors," *Anti-Cancer Drugs*, 12 (9): 713-717, 2001.
- McGeer and McGeer, "The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases," *Brain Research Reviews*, 21:195-218, 1995.
- Mehta et al., "Activation of retinoid receptors RAR alpha and RXR alpha induces differentiation and apoptosis, respectively, in HL-60 cells," *Cell, Growth Differ.*, 7(2): 179-186, 1996.
- Melichar et al., "Growth-inhibitory effect of a novel synthetic triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, on ovarian carcinoma cell lines not dependent on peroxisome proliferator-activated receptor-gamma expression," *Gynecologic Oncology*, 93:149-154, 2004.
- Melia et al., "1, 2-dideoxy-3, 4:5, 7-bis-o-(1-methylethylidene)-D-glucosyl- and -D-galacto-hept-1-ynitols: synthesis and conformational studies," *Tetrahedron*, 44:1673-1678, 1988.
- Meng et al., "A diterpenoid with a new carbon skeleton from *Pygmaeopremna herbacea*," *Phytochemistry*, 27 (4): 1151-1152, 1988.
- Meng et al., "RV09, a novel resveratrol analogue, inhibits NO and TNF-alpha production by LPS-activated microglia," *International Immunopharmacology*, 8 (8): 1074-1082, 2008.
- Merril and Benveniste, "Cytokines in inflammatory brain lesions: helpful and harmful," *Trends Neurosci.*, 19:331-338, 1996.
- Miller and Shi, "Formation of 2,3-dehydro-1,2-dihydro-1,1-dimethylnaphthalene, 'isoaromatic' molecule," *J. of the American Chemical Society*, 109 (2): 578-579, 1987.
- Miller and Shi, "Novel rearrangement and cyclization processes resulting from bromination of 1,1-dibenzyltetralin derivatives," *Journal of Organic Chemistry*, 57 (6): 1677-1681, 1992.
- Minghetti et al., "Production of diterpenoids by *Euphorbia calytrata* cell cultures," *Phytochemistry*, 42 (6): 1587-1589, 1996.
- Minns et al., "A novel triterpenoid induces transforming growth factor beta production by intraepithelial lymphocytes to prevent ileitis," *Gastroenterology*, 127:119-126, 2004.
- Mix et al., "A synthetic triterpenoid selectively inhibits the induction of matrix metalloproteinases 1 and 13 by inflammatory cytokines," *Arthritis Rheum.*, 44:1096-1104, 2001.
- Mix et al., "Peroxisome proliferator-activated receptor-gamma-independent repression of collagenase gene expression by 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid and prostaglandin 15-deoxy-delta(12,14) J2: a role for Smad signaling," *Mol. Pharmacol.*, 65:309-318, 2004.
- Moncada et al., "Nitric oxide: physiology, pathophysiology, and pharmacology," *Pharmacol. Rev.*, 43:109-142, 1991.
- Mori et al., "Further preparation of steroidal diospenols. I. Synthesis of some 4,4-dimethyl-2-hydroxy-3-oxo-1-ene steroids in androstane and pregnane series," *Chemical and Pharmaceutical Bulletin*, 16 (9): 1795-1801, 1968.
- Mori et al., "Synthesis of 4,4-dimethyl-2-nitro-5 α -cholest-1-en-3-one," *Chemical and Pharmaceutical Bulletin*, 30 (12): 4516-4517, 1982.
- Morris et al., "Association of a functional inducible nitric oxide synthase promoter variant with complications in type 2 diabetes," *J. Mol. Med.*, 80 (2): 96-104, 2002.
- Morse and Choi, "Heme oxygenase-1: from bench to bedside," *Am. J. Respir. Crit. Care Med.*, 172 (6): 660-670, 2005.
- Morse and Choi, "Heme oxygenase-1: the 'emerging molecule' has arrived," *Am. J. Respir. Crit. Care Med.*, 27(1):8-16, 2002.
- Morzycki and Wilczewska, "Reactions of 4-azacholest-5-en-3-one, 6-azacholest-4-en-7-one, and their N-methyl derivatives with electrophilic reagents," *Tetrahedron*, 52 (44): 14057-14068, 1996.
- Murphy et al., "Immunomodulatory Effects of the Triterpenoid CDDO after Allogeneic Bone Marrow Transplantation in Mice: Reduction of Acute Graft-Versus-Host Disease Lethality," *Blood*, 106:1316, 2005.
- Murray and Zweifel, "Preparation of Phenyl Cyanate and Its Utilization for the Synthesis of α , β -Unsaturated Nitriles," *Synthesis*, 150-151, 1980. *Synthesis*, 150-151, 1980.
- Muzart, "Synthesis of unsaturated carbonyl compounds via a chromium-mediated allylic oxidation by 70% tert-butylhydroperoxide," *Tetrahedron Lett.*, 28:4665-4668, 1987.
- Na and Surh et al., "Transcriptional regulation via cysteine thiol modification: a novel molecular strategy for chemoprevention and cytoprotection," *Mol. Carcinog.*, 45 (6): 368-380, 2006.
- Nanduri et al., "Biological investigation and structure-activity relationship studies on azadirone from *Azadirachta indica* A. juss.," *Bioorganic and Medicinal Chemistry*, 13 (22): 4111-4115, 2003.
- Nathan and Xie, "Nitric oxide synthases: roles, tolls, and controls," *Cell*, 78:915-918, 1994.
- Nathan et al., "Protection from Alzheimer's-like disease in the mouse by genetic ablation of inducible nitric oxide synthase," *The Journal of Experimental Medicine*, 202:1163-1169, 2005.
- Nathan, "Points of control in inflammation," *Nature*, 420:846-852, 2002.
- Nelson et al., "Oxidative demethylation at C-4 of a steroid via nitroxide photolysis," *J. of the American Chemical Society*, 97 (3): 648-649, 1975.
- Nicholson et al., "Lethality of endotoxin in mice genetically deficient in the respiratory burst oxidase, inducible nitric oxide synthase, or both," *Shock*, 11:253-258, 1999.

(56)

References Cited

OTHER PUBLICATIONS

- Nishino et al., "Inhibition of the tumor-promoting action of 12-O tetradecanoylphorbol-13-acetate by some oleanane-type triterpenoid compounds," *Cancer Res.*, 48:5210-5215, 1988.
- Notice of Allowance issued in U.S. Appl. No. 12/426,889, dated Apr. 27, 2012.
- Office Action issued in New Zealand application No. 588708, dated Mar. 30, 2011.
- Office Communication issued in Singapore Patent Application No. 201007606-5, dated May 3, 2012.
- Office Communication issued in U.S. Appl. No. 12/426,889, dated Jul. 19, 2011.
- Office Communication issued in U.S. Appl. No. 12/426,889, dated Dec. 21, 2011.
- Ohshima and Bartsch, "Chronic infections and inflammatory process as cancer risk factors: possible role of nitric oxide in carcinogenesis," *Mutat. Res.*, 305:253-264, 1994.
- Omura and Swern, "Oxidation of Alcohols by 'Activated' Dimethyl Sulfoxide. A Preparative, Steric and Mechanistic Study," *Tetrahedron*, 34:1651-1660, 1978.
- Ono et al., "A convenient procedure for esterification of carboxylic acids," *Bull. Chem. Soc. Jpn.*, 51:2401-2404, 1978.
- Orr et al., "Steroids, CCLXV. Studies in cyano steroids. III. Unsaturated 2-cyano steroids," *J. Org. Chem.*, 29(11): 3300-3303, 1964.
- Osburn et al., "Genetic of pharmacologic amplification of Nrf2 signaling inhibits acute inflammatory liver injury in mice," *Toxicological Sciences*, 104:218-227, 2008.
- Oshima et al., "Suppression of intestinal polyposis in Apc^{Δ716} knock-out mice by inhibition of cyclooxygenase 2 (COX-2)," *Cell*, 87:803-809, 1996.
- Overnell and Whitehursts, "Reactions of steroid A-ring lactones with Grignard reagents," *J. of the Chemical Society [Section] C: Organic*, 2: 378-384, 1971.
- Pahl, "Activators and target genes of Rel/NF-κB transcription factors," *Oncogene*, 18:6853-6866, 1999.
- Palcy and Goltzman, "Protein kinase signalling pathways involved in the up-regulation of the rat alpha1(I) collagen gene by transforming growth factor beta1 and bone morphogenetic protein 2 in osteoblastic cells," *Biochem. J.*, 343:21-27, 1999.
- Pappas et al., "Photoisomerization of phenalen-1-one oxide. New course of light-induced alpha beta-epoxy ketone rearrangement," *J. of the American Chemical Society*, 92 (19): 5797-5798, 1970.
- Parra-Delgado et al., "Synthesis and comparative molecular field analysis (CoMFA) of argentatin B derivatives as growth inhibitors of human cancer cell lines," *Bioorganic & Medicinal Chemistry*, 14 (6): 2006.
- Patel et al., "Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation," *J. Clin. Oncol.*, 19 (15): 3483-3489, 2001.
- Paul et al., "Design and synthesis of a self-assembled photochemical dyad based on selective imidazole recognition," *Inorg. Chem.*, 41:3699-3704, 2002.
- Paul et al., "Effective expression of small interfering RNA in human cells," *Nature Biotechnol.*, 20:505-508, 2002.
- PCT International Preliminary Report on Patentability issued in International Application No. PCT/US2009/041177, mailed Oct. 28, 2010.
- PCT International Search Report and Written Opinion issued in International Application No. PCT/US2009/041177, mailed Jan. 21, 2010.
- PCT Invitation to Pay Additional Fees issued in International Application No. PCT/US2009/041177, mailed Aug. 31, 2009.
- Pedersen et al., "The triterpenoid CDDO induces apoptosis in refractory CLL B cells," *Blood*, 100:2965-2972, 2002.
- Piacenza et al., "A new atisane diterpene: *ent*-16α-hydroxyatis-13-en-3-one from *Androstachys johnsonii* prain," *J. of the Chemical Society, Perkins Transactions 1: Organic and Bio-Organic Chemistry*, 4: 703-709, 1985.
- Piacenza et al., "Beyerane diterpenes: structure and reactivity of the α-ketol *ent*-3β-hydroxybeyer-15-ene-2,12-dione, its corresponding diosphenol, and synthesis of the isomeric α-ketol acetates," *J. of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry*, 4: 1004-1012, 1979.
- Picard et al., "The triterpene resinols and related acids, part VI," *J. Chem. Soc.*, 1045-108, 1939.
- Place et al., "The novel synthetic triterpenoid, CDDO-imidazolide, inhibits inflammatory response and tumor growth in vivo," *Clin. Cancer Res.*, 9:2798-2806, 2003.
- Pletnev et al., "Carbopalladation of nitriles: Synthesis of 2,3-diarylindenones and polycyclic aromatic ketones by the Pd-catalyzed annulation of alkynes and bicyclic alkenes by 2-iodoarenenitriles," *J. of Organic Chemistry*, 67 (26): 9276-9287, 2002.
- Pollard, "Tumour-educated macrophages promote tumour progression and metastasis," *Nature Reviews*, 4:71-78, 2004.
- Prescott and White, "Self-promotion? Intimate connections between APC and prostaglandin H synthase-2," *Cell*, 87:783-786, 1996.
- Rangasamy et al., "Disruption of Nrf2 enhances susceptibility to severe airway inflammation and asthma in mice," *Journal of Experimental Medicine*, 202:47-59, 2005.
- Rasmusson et al., "Azasteroids: structure-activity relationships for inhibition of 5 alpha-reductase and of androgen receptor binding," *J. Med. Chem.*, 29 (11): 2298, 1986.
- Rayet and Gelinas, "Aberrant rel/nfkb genes and activity in human cancer," *Oncogene*, 18:6938-6947, 1999.
- Reddy et al., "Evaluation of cyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis," *Cancer Res.*, 56(20):4566-4569, 1996.
- Response to Office Communication issued in U.S. Appl. No. 12/426,889, dated Oct. 19, 2011.
- Response to Office Communication issued in U.S. Appl. No. 12/426,889, dated Mar. 21, 2012.
- Richardson et al., "Synthesis and restriction enzyme analysis of oligodeoxyribonucleotides containing the anti-cancer drug 2',2'-difluoro-2'-deoxycytidine," *Nucleic Acid Res.*, 20 (7): 1763-1769, 1992.
- Rizzieri et al., "Phase I evaluation of prolonged-infusion gemcitabine with mitoxantrone for relapsed or refractory acute leukemia," *J. Clin. Oncol.*, 20 (3): 674-679, 2002.
- Robbins et al., "Inflammation and Repair," In: Basic Pathology 3rd Edition, W.B. Saunders Company, Chapter 2, p. 28, 1981.
- Rossi et al., "Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of IkappaB kinase," *Nature*, 403:103-108, 2000.
- Ruvolo et al., "The novel triterpenoid methyl-CDDO inhibits Bcl2 phosphorylation and potently kills U937 cells," *Blood*, 94(10), Suppl. 1, Part 1: 280A, abstract #1251, 1999.
- Sacerdoti et al., "Heme oxygenase overexpression attenuates glucose-mediated oxidative stress in quiescent cell phase: linking heme to hyperglycemia complications," *Curr. Neurovasc. Res.*, 2(2): 103-111, 2005.
- Salvemini et al., "Endogenous nitric oxide enhances prostaglandin production in a model of renal inflammation," *J. Clin. Invest.*, 93(5):1940-1947, 1994.
- Salvemini et al., "Nitric oxide activates cyclooxygenase enzymes," *Proc. Natl. Acad. Sci. USA*, 90(15):7240-7244, 1993.
- Samudio et al., "2-cyano-3,12 dioxoolean-1,9 diene-28-imidazolide induces apoptosis in pancreatic cancer via redox-dependent cytoplasmic stress," *Proc. Amer. Assoc. Cancer Res.*, 46: Abstract No. 5899, 2005.
- Samudio et al., "2-Cyano-3,12-dioxooleana-1,9-dien-28-imidazolide (CDDO-Im) directly targets mitochondrial glutathione to induce apoptosis in pancreatic cancer," *J. Biol. Chem.*, 280:36273-36282, 2005.
- Samudio et al., "A novel mechanism of action of methyl-2-cyano-3,12 dioxoolean-1,9 diene-28-oate: direct permeabilization of the inner mitochondrial membrane to inhibit electron transport and induce apoptosis," *Mol. Pharmacol.*, 69:1182-1193, 2006.
- Samudio et al., "A novel mechanism of action of methyl-2-cyano-3,12 dioxoolean-1,9 diene-28-oate (CDDO-Me): Direct permeabilization of the inner mitochondrial membrane to inhibit electron transport and induce apoptosis," *Proc. Am. Assoc. Cancer Res.*, 47: Abstract No. 4693, 2006.

(56)

References Cited

OTHER PUBLICATIONS

- Samudio et al., "The novel triterpenoid CDDOme potently synergizes with inhibition of bcl-2 function to induce apoptosis in AML via disruption of intracellular redox homeostasis," *Proc. Amer. Assoc. Cancer Res.*, 46: Abstract No. 4955, 2005.
- Satoh et al., "Activation of the Keap1/Nrf2 pathway for neuroprotection by electrophilic [correction of electrophilic] phase II inducers," *PNAS*, 103 (3): 768-773, 2006.
- Scholz et al., "Sensitive and specific methods for the determination of CDDO methyl ester in mouse, rat, dog, monkey, and human plasma by LC-tandem mass spectrometry," *Proc. Amer. Assoc. Cancer Res.*, 4: Abstract No. 6321, 2003.
- Schulz et al., "Nitric oxide, tetrahydrobiopterin, oxidative stress, and endothelial dysfunction in hypertension," *Antioxid. Redox. Sig.*, 10 (6):1115-1126, 2008.
- Seibert and Masferrer, "Role of inducible cyclooxygenase (COX-2) in inflammation," *Receptor*, 4(1):17-23, 1994.
- Sharpless et al., "Electrophilic and nucleophilic organoselenium reagents. New routes to alpha, beta-unsaturated carbonyl compounds," *J. Am. Chem. Soc.*, 95:6137, 1973.
- Sheng et al., "A selective cyclooxygenase 2 inhibitor suppresses the growth of H-ras-transformed rat intestinal epithelial cells," *Gastroenterology*, 113(6):1883-1889, 1997.
- Sheng et al., "Inhibition of human colon cancer cell growth by selective inhibition of cyclooxygenase-2," *J. Clin. Invest.*, 99(9):2254-2259, 1997.
- Shishodia et al., "A synthetic triterpenoid, CDDO-Me, inhibits IkappaBalpha kinase and enhances apoptosis induced by TNF and chemotherapeutic agents through down-regulation of expression of nuclear factor kappaB-regulated gene products in human leukemic cells," *Clin. Cancer Res.*, 12:1828-1838, 2006.
- Shull et al., "Identification of a vitamin D-responsive protein on the surface of human osteosarcoma cells," *Proc. Natl. Acad. Sci. USA*, 86:5405-5410, 1989.
- Shull et al., "Morphologic and biochemical studies of canine mucopolysaccharidosis I," *Am. J. Pathol.*, 114:487-495, 1984.
- Simonian and Coyle, "Oxidative stress in neurodegenerative diseases," *Annu. Rev. Pharmacol. Toxicol.*, 36:83-106, 1996.
- Simonsen et al., "Tetracyclic hydroxy acids," in *the Terpenes*, Cambridge University, Cambridge, 5:221-285, 1957.
- Singh and Evans, "Nitric oxide, the biological mediator of the decade: fact or fiction?" *Eur. Respir. J.*, 10:699-707, 1997.
- Singh et al., "Anti-inflammatory activity of oleanolic acid in rats and mice," *J. Pharm. Pharmacol.*, 44:456-458, 1992.
- Sive et al., "Expression of chondrocyte markers by cells of normal and degenerate intervertebral discs," *Mol. Pathol.*, 55:91-97, 2002.
- Snitman et al., "Tetracyclic hydroxy acids to taxodione synthesis of methyl 12-oxopodocarpa-5,9(11)-diene-8β-carboxylate," *Synth. Comm.*, 8:187-194, 1978.
- Sonogashira et al., "A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes, and bromopyridines," *Tetrahedron Lett.*, 4467-4470, 1975.
- Sporn and Roberts, "Peptide growth factors and inflammation, tissue repair, and cancer," *J. Clin. Invest.*, 78:329-332, 1986.
- Sporn et al., "Prospects for prevention and treatment of cancer with selective PPARγ modulators (SPARMs)," *Trends in Molecular Medicine*, 7(9):395-400, 2001.
- Sporn et al., "Transforming growth factor-beta: biological function and chemical structure," *Science*, 233:532-534, 1986.
- Stadheim et al., "The novel triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) potently enhances apoptosis induced by tumor necrosis factor in human leukemia cells," *J. Biol. Chem.*, 277:16448-16455, 2002.
- Steadman's Medical Journal 23rd Edition, The Williams & Wilkins Company, p. 401, 1976.
- Sterzycki, "Pyrocinium tosylate, a mild catalyst for formation and cleavage of dioxolane-type acetals," *Synthesis*, 724-725, 1979.
- Stewart et al., "Risk of Alzheimer's disease and duration of NSAID use" *Neurology*, 48:626-632, 1997.
- Stork et al., "A stereospecific total synthesis of 18-substituted steroids. Application to the synthesis of dl-conessine," *J. of the American Chemical Society*, 84: 2018-2020, 1962.
- Strejan et al., "Suppression of chronic-relapsing experimental allergic encephalomyelitis in strain-13 guinea pigs by administration of liposome-associated myelin basic protein," *J. Neuroimmunol.*, 7 (1): 27, 1984.
- Suginome et al., "The photochemistry of steroidal 6-membered cyclic α-nitro ketones," *Bulletin of the Chemical Society of Japan*, 61 (11): 4005-4014, 1988.
- Suh et al., "A novel synthetic oleanane triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, with potent differentiating, antiproliferative, and anti-inflammatory activity," *Cancer Res.*, 59(2):336-341, 1999.
- Suh et al., "A novel synthetic oleanane triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO), induces cell differentiation in human myeloid leukemias," *Proceedings of the American Association for Cancer Research Annual Meeting*, 40:300, abstract # 1988, 1999.
- Suh et al., "New triterpenoids as cancer preventive and anti-inflammatory agents," *Proceedings of the American Association for Cancer Research*, Abstract No. 1457, 38: 216, 1997.
- Suh et al., "Novel triterpenoids suppress inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2) in mouse macrophages," *Cancer Research*, 58:717-723, 1998.
- Suh et al., "Novel triterpenoids suppress inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2)," *Proceedings of the American Association for Cancer Research Annual Meeting*, 39: Abstract No. 1821, 1998.
- Suh et al., "Synthetic triterpenoids activate a pathway for apoptosis in AML cells involving downregulation of FLIP and sensitization to TRAIL," *Leukemia*, 17:2122-2129, 2003.
- Suh et al., "Synthetic triterpenoids enhance transforming growth factor β/Smad signaling," *Cancer Res.*, 63:1371-1376, 2003.
- Suh et al., "Triterpenoids CDDO and CDDO-Me Down-Regulate FLIP Expression and Sensitize AML Cells to Trail-Induced Apoptosis," *American Society of Hematology 43rd Annual Meeting and Exposition*, Abstract No. 498, 2001.
- Sun et al., "The synthetic triterpenoid, CDDO, suppresses alloreactive T cell responses and reduces murine early acute graft-versus-host disease mortality," *Biology of Blood and Marrow Transplantation*, 13:521-529, 2007.
- Sussan et al., "Disruption of Nrf2, a key inducer of antioxidant defenses, attenuates ApoE-mediated atherosclerosis in mice," *PLoS One*, 3 (11): 1-9, 2008.
- Syftestad et al., "The in vitro chondrogenic response of limb-bud mesenchyme to a water-soluble fraction prepared from demineralized bone matrix," *Differentiation*, 29:230, 1985.
- Tabe et al., "Chromatin-Mediated Transcriptional Activation with Novel Peroxisome Proliferator-Activated Receptor gamma (PPARγ) Ligand 2-cyano-1,9-dien-28-oic acid (CDDO) in Acute Promyelocytic Leukemia Cells," *Abstracts of the 44th Annual Meeting of the American Society of Hematology*, Abstract No. 2191, 2002.
- Takabe et al., "Synthesis of lycosyl esters of oleanolic," *Carbohydrate Research*, 76:101-108, 1979, Database CAPLUS on STN AN:1980:42278.
- Takahashi et al., "Increased expression of inducible and endothelial constitutive nitric oxide synthases in rat colon tumors induced by azoxymethane," *Cancer Res.*, 57:1233-1237, 1997.
- Takeda et al., "Orthosiphon D and E, minor diterpenes from *Orthosiphon stamineus*," *Phytochemistry*, 33 (2): 411-415, 1993.
- Tamir and Tannebaum, "The role of nitric oxide (NO) in the carcinogenic process," *Biochim. Biophys. Acta*, 1288:F31-F36, 1996.
- Tamm et al., "Expression and prognostic significance of IAP-family genes in human cancers and leukemias," *Blood*, 94(Suppl. 1):69a, Abstract # 298, 1999.
- Tan et al., "Survey on the triterpenoids from *rubus l.* and their spectral features," *Huagong Shikan*, 18 (9): 1-4, 2004.
- Tempero et al., "Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma," *J. Clin. Oncol.*, 21 (18): 3402-3408, 2003.

(56)

References Cited

OTHER PUBLICATIONS

- Tenenbaum and Heersche, "Differentiation of osteoblasts and formation of mineralized bone in vitro," *Calcif. Tissue Int.*, 34:76, 1982.
- Therasse et al., "New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada," *J. Natl. Cancer Instit.*, 92(3): 205, 2000.
- Thimmulappa et al., "Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis," *J. Clinical Investigation*, 116(4): 984-995, 2006.
- Thimmulappa et al., "Nrf2-dependent protection from LPS induced inflammatory response and mortality by CDDO-imidazolide," *Biochem. Biophys. Res. Commun.*, 351:883-889, 2006.
- Thimmulappa et al., "Preclinical evaluation of targeting the Nrf2 pathway by triterpenoids (CDDO-Im and CDDO-Me) for protection from LPS-induced inflammatory response and reactive oxygen species in human peripheral blood mononuclear cells and neutrophils," *Antioxidants & Redox Signaling*, 9:1-8, 2007.
- Tian et al., "Carbopalladation of nitriles: synthesis of 3,4-disubstituted 2-aminonaphthalenes and 1,3-benzoxazine derivatives by the palladium-catalyzed annulation of alkynes by (2-Iodophenyl)acetonitrile," *J. of Organic Chemistry*, 68(2): 339-347, 2003.
- Tinto et al., "Terpenoid constituents of *Oxandra asbeckii*," *Journal of Natural Products*, 55(6): 701-706, 1992.
- Toriumi et al., "Mandibular reconstruction with a recombinant bone-inducing factor. Functional, histologic, and biomechanical evaluation," *Arch. Otolaryngol. Head Neck Surg.*, 117:1101-1112, 1991.
- Torres et al., "Inflammation and nitric oxide production in skeletal muscle of type 2 diabetic patients," *Journal of Endocrinology*, 181:419-427, 2004.
- Tran et al., "The synthetic triterpenoid CDDO-methyl ester modulates microglial activities, inhibits TNF production, and provides dopaminergic neuroprotection," *Journal of Neuroinflammation*, 5:1-14, 2008.
- Tsai et al., "Monoclonal antibody to human osteosarcoma: a novel Mr 26,000 protein recognized by murine hybridoma TMMR-2," *Cancer Res.*, 50:152-161, 1990.
- Tsao et al., "DRIP205 co-activator overexpression enhances PPARGgamma-mediated differentiation of leukemia cells by CDDO," *Proc. Amer. Assoc. Cancer Res.*, 46: Abstract No. 1855, 2005.
- Tsao et al., "Targeted Induction of Apoptosis in Leukemias by PPARGgamma Ligation," *American Society of Hematology 43rd Annual Meeting and Exposition*, Abstract No. 2381, 2001.
- Tsujii and DuBois, "Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2," *Cell*, 83(3):493-501, 1995.
- Tsujii et al., "Cyclooxygenases regulates angiogenesis induced by colon cancer cells," *Cell*, 93:705-716, 1998.
- Turksen et al., "Isolation of monoclonal antibodies recognizing rat bone-associated molecules in vitro and in vivo," *J. Histochem. Cytochem.*, 40:1339-1352, 1992.
- Urban et al., "Influence of esterification and modification of A-ring in a group of lupane acids on their cytotoxicity," *Bioorganic and Medicinal Chemistry*, 13(19): 5527-5535, 2005.
- Urban et al., "Synthesis of A-seco derivatives of betulinic acid with cytotoxic activity," *J. of Natural Products*, 67(7): 1100-1105, 2004.
- Uskoković et al., "D-Homosteroids. I. 3 β -Hydroxy-17 α ,17 α -dimethyl-D-homoandrostane-17-one and related compounds," *J. of the American Chemical Society*, 81: 4561-4566, 1959.
- Van Muiswinkel and Kuiperij, "The Nrf2-ARE signaling pathway: promising drug target to combat oxidative stress in neurodegenerative disorders," *Current Drug Target—CNS & Neurological Disorders*, 4:267-281, 2005.
- Vazquez et al., "Human immunodeficiency virus type 1-induced macrophage gene expression includes the p21 gene, a target for viral regulation," *J. Virol.*, 79:4479-4491, 2005.
- Veerman et al., "Antitumor activity of prolonged as compared with bolus administration of 2',2'-difluorodeoxycytidine in vivo against murine colon tumors," *Cancer Chemother. Pharmacol.*, 38(4): 335-342, 1996.
- Vodovotz et al., "Inducible nitric oxide synthase in tangle-bearing neurons of patients with Alzheimer's Disease," *The Journal of Experimental Medicine*, 184:1425-1433, 1996.
- Vukicevic et al., "Stimulation of the expression of osteogenic and chondrogenic phenotypes in vitro by osteogenin," *Proc. Natl. Acad. Sci. USA*, 86:8793-7, 1989.
- Wada et al., "Synthetic lanostane-type triterpenoids as inhibitors of DNA topoisomerase II," *Bioorganic & Medicinal Chemistry Letters*, 15(12): 2005.
- Walczak et al., "Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo," *Nature Medicine*, 5(2):157-163, 1999.
- Walsh et al., "Monoclonal antibodies with selective reactivity against osteoblasts and osteocytes in human bone," *J. Bone Miner Res.*, 9:1687-1696, 1994.
- Wang et al., "A novel synthetic triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) induces adipocyte differentiation in 3T3-L1 cells," *Proceedings of the American Association for Cancer Research Annual Meeting*, 40:300, abstract # 1989, 1999.
- Wang et al., "A synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), is a ligand for the peroxisome proliferator-activated receptor γ ," *Mol. Endocrin.*, 14(10):1550-1556, 2000.
- Wang et al., "Diterpenoids from roots of *Euphorbia wallichii*," *Zhongcaoyao*, 35(6): 611-614, 2004.
- Wang et al., "Synthetic triterpenoid CDDO and its derivatives increase ceramides and are cytotoxic to pediatric acute lymphoblastic leukemia cell lines," *Proc. Am. Assoc. Cancer Res.*, 47: 4643, 2006.
- Warrell et al., "Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid)," *N. Engl. J. Med.*, 324(20):1385-1393, 1991.
- Wen et al., "Pentacyclic triterpenes. Part 2: Synthesis and biological evaluation of maslinic acid derivatives as glycogen phosphorylase inhibitors," *Bioorganic and Medicinal Chemistry Letters*, 16(3): 722-726, 2006.
- Williams et al., "Immunology of multiple sclerosis," *Clin. Neurosci.*, 2(3-4):229-245, 1994.
- Woodley, "Liposomes for Oral Administration of Drugs," *Crit. Rev. Therapeutic Drug Carrier System*, 2(1):1-18, 1995.
- Wulff et al., "The Natural Product Avrainvillamide Binds to the Oncoprotein Nucleophosmin," *J. of the American Chemical Society*, 129(46): 14444-14451, 2007.
- Xie et al., "Differential expression patterns in human myeloblastic leukemia HL-60 and multidrug resistant HL-60/Dox cells analyzed by human cDNA expression array," *Blood*, 92 (Suppl 1):387a, Abstract #1600, 1998.
- Yates et al., "Pharmacodynamic characterization of chemopreventive triterpenoids as exceptionally potent inducers of Nrf2-regulated genes," *Mol. Cancer Ther.*, 6:154-162, 2007.
- Yates et al., "Potent protection against aflatoxin-induced tumorigenesis through induction of Nrf2-regulated pathways by the triterpenoid 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole," *Cancer Res.*, 66:2488-2494, 2006.
- Yore et al., "The synthetic triterpenoid 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole blocks nuclear factor-kappaB activation through direct inhibition of IkappaB kinase beta," *Mol. Cancer Ther.*, 5(12): 3232-3239, 2006.
- You et al., "Synthesis and cytotoxic activity of a-ring modified betulinic acid derivatives," *Bioorganic and Medicinal Chemistry Letters*, 13(19): 3137-3140, 2003.
- Yu and Kensler, "Nrf2 as a target for cancer chemoprevention," *Mutat. Res.*, 591(1-2): 93-102, 2005.
- Yue et al., "Depletion of intracellular glutathione contributes to JNK-mediated death receptor 5 upregulation and apoptosis induction by the novel synthetic triterpenoid methyl-2-cyano-3, 12-dioxooleana-1, 9-dien-28-oate (CDDO-Me)," *Cancer & Biology Therapy*, 5(5):492-497, 2006.
- Zapata et al., "CDDO and CDDO-Im Reduce Tumor Burden in a Transgenic Mouse Model of CLL," *Blood*, 104:3477, 2004.

(56)

References Cited

OTHER PUBLICATIONS

- Zapata et al., "Triterpenoids show activity against leukemic cells in a transgenic mouse model of CLL," *Proc. Amer. Assoc. Cancer Res.*, 46: Abstract No. 5179, 2005.
- Zhang et al., "Synthetic triterpenoid CDDO as effective therapy for HER2-expressing resistant breast cancer," *Proc. Amer. Assoc. Cancer Res.*, Abstract No. 3799, 2004.
- Zhang et al., "The novel synthetic oleanane triterpenoid CDDO (2-cyano-3, 12-dioxoolean-1, 9-dien-28-oic acid) induces apoptosis in Mycosis fungoides/Sézary syndrome cells," *J. Invest. Dermatol.*, 123:380-387, 2004.
- Zhou et al., "Carbon monoxide suppresses bleomycin-induced lung fibrosis," *Am. J. Pathol.*, 166 (1): 27-37, 2005.
- Zhou et al., "Physical stability of amorphous pharmaceuticals: Importance of configurational thermodynamic quantities and molecular mobility," *J. Pharmaceutical Sciences*, 91 (8): 1863-1872, 2002.
- Zoretic et al., "Advanced Tetracycles in a Stereoselective Approach to d,l-Spongistriol and Related Metabolites: The Use of Radicals in the Synthesis of Angular Electrophores," *J. Organic Chemistry*, 63:1162-1167, 1998.
- Zou et al., "c-Jun NH2-terminal kinase-mediated up-regulation of death receptor 5 contributes to induction of apoptosis by the novel synthetic triterpenoid methyl-2-cyano-3,12-dioxooleana-1, 9-dien-28-oate in human lung cancer cells," *Cancer Res.*, 64:7570-7578, 2004.
- Zundel et al., "Backbone rearrangement of A-noreuphenone," *Bulletin de la Societe Chimique de France*, 11 Part 2: 3206-3208, 1973.
- Bai, et al., "Modified compounds from ursolic acid and their antitumor activities", *Huaxi Yaoxue Zazhi*, 18(2):87-90, 2003 (Chinese, English Abstract).
- Barton, et al., "The synthesis of β -amyrin", *Journal of the Chemical Society*, 1031-1040, 1968.
- Ganguly, et al., "Chemical constituents of *Glochidion hohenackeri*", *Tetrahedron*, 22:1513-1519, 1966.
- PCT International Search Report and Written Opinion issued for International Application No. PCT/US2013/045975, issued Sep. 24, 2013.
- Aghoramurthy, et al., "Structure of cedrelone", *J. Sci. Ind. Res.*, 1962, 21B:95-96.
- Akiyama, et al., "Cell mediators of inflammation in the Alzheimer disease brain", *Alzheimer Dis. Assoc. Disord.*, 2000, 14(1): S47-S53.
- Albini and Sporn, "Opinion: the tumour microenvironment as a target for chemoprevention", *Nature Reviews Cancer*, 2002, Abstract 501:149.
- Ballesta-Acosta, et al., "A new 24-nor-oleanane triterpenoid from *Salvia carduacea*", *J. Nat. Prod.*, 2002, 65(10):1513-1515.
- Bowden, et al., "Constituents of the fruit of pseudopanax arboreum (Araliaceae)", *Australian Journal of Chemistry*, 1975, 28(1):91-107.
- Breen, et al., "The chemical constituents of Australian *Flindersia* species. XIX. Triterpenoids from the leaves of *F. bourjotiana*", *Australian J. Chem.*, 1966, 19(3):455-481.
- Buchanan, et al., "The conversion of turraeanthin and turraeanthin A into simple melaiacins by a route involving an oxidative rearrangement of porbale biogenetic importance", *J. Chem. Soc. C*, 1970, 17:2280-2284.
- Buchanan, et al., "The synthesis of the simplest mealicins (limonoids) from tetranortirucallen triterpenoids containing a beta-substituted furyl side-chain", *Chemical Communications*, 1969, 5:242-243.
- Cardona, et al., "Synthesis of Natural Polyhydroxystilbenes", *Tetrahedron*, 1986, 42(10):2725-2730.
- Chaudhry and Jones, "The chemistry of the triterpenes and related compounds. Part XXXIX. Some derivatives of 4,4-dimethylcholestan-3-one", *J. of the Chemical Society*, 1961, 2725-2732.
- Cohen, et al., "A general method for removal of a 4-methyl group from triterpenoids. Synthesis of 4beta-demethylglycyrrhetinic acid", *J. Chem. Soc. Perkin Trans. 1*, 1973, 19:2076-2082.
- Connolly, et al., "Grandiofolione: a novel tetranortriterpenoid", *Chemical Communications*, 1966, 23:567-568.
- Couch, et al., "2-cyano-3,12-dioxooleana-1,9(11)-diene-28-oic Acid Disrupts Microtubule Polymerization: A Possible Mechanism Contributing to Apoptosis", *Molecular Pharmacology*, 2006, 69:1158-1165.
- Couch, et al., "Studies on the reactivity of CDDO, a promising new chemopreventive and chemotherapeutic agent: implications for a molecular mechanism of action", *Bioorganic and Medicinal Chemistry Letters*, 2005, 15(9):2215-2219.
- Damsté, et al., "A sedimentary tetrahydrophenanthrene derivative of tetrahymanol", *Tetrahedron Letters*, 1999, 40(20):3949-3952.
- Dinkova-Kostova, et al., "Direct evidence that sulfhydryl groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants", *Proc. Natl. Acad. Sci.*, 2002, 99(18):11908-11913.
- Dirsch, et al., "The triterpenoid quinomethide pristimerin inhibits induction of inducible nitric oxide synthase in murine macrophages", *Eur. J. Pharmacol.*, 1997, 336(2-3):211-217.
- Dracinsky, et al., "Preparation and Conformational Study of 19 β ,28-Epoxy-18 α -olean-5-ene derivatives", *Collection of Czechoslovak Chemical Communications*, 2006, 71(3):387-410.
- Duan, et al., "Di- and triterpenoids from *Tripterium hypoglaucom* Phytochemistry", *Phytochemistry*, 1997, 46(3):535-543.
- Finlay, et al., "Novel A-ring cleaved analogs of oleanolic and ursolic acids which affect growth regulation in NRP.152 prostate cells", *Bioorg. Med. Chem. Lett.*, 1997, 7(13):1769-1772.
- Finlay, et al., "The Effect of A and C Ring Modification of Oleanolic and Ursolic Acid on the Inhibition of Nitric Oxide Formation in Mouse Macrophages", 213th American Chemical Society National Meeting, Abstract:084, 1997.
- Gao, et al., "Synthetic triterpenoids inhibit growth and induce apoptosis in human glioblastoma and neuroblastoma cells through inhibition of prosurvival Akt, NF- κ B and Notch1 signaling", *J. of Neurooncology*, 2007, 84(2):147-157.
- Han, et al., "CDDO-Imidazolidine inhibits growth and survival of c-Myc-induced mouse B cell and plasma cell neoplasms", *Molecular Cancer*, 2006, 5:22.
- Honda, et al., "New synthetic oleanane and ursane triterpenoids as inhibitors of nitric oxide production in mouse macrophages", The Fifth Chemical Congress of North America, Cancun, Mexico, Abstract 552 and slides for oral presentation, Nov. 1997.
- Ikeda, et al., "Triterpenoid CDDO-Im downregulates PML/RAR α expression in acute promyelocytic leukemia cell", *Cell Death and Differentiation*, 2005, 12(5):523-531.
- Inoue, et al., "CDDO induces apoptosis via the intrinsic pathway in lymphoid cells", *Leukemia*, 2004, 18(5):948-952.
- Jang, et al., "24-nor-ursane type triterpenoids from the stems of *Rumex japonicus*", *Chem. Pharm. Bull* (Tokyo), 2005, 53(12):1594-1596.
- Ji, et al., "The synthetic triterpenoid CDDO-imidazolidine induces monocytic differentiation by activating the Smad and ERK signaling pathways in HL60 leukemia cells", *Molecular Cancer Therapeutics*, 2006, 5(6):1452-1458.
- Kamal, et al., "23-oxoisopristimerin III: an new natural phenolic (9 \rightarrow 8)-24-nor-D:A-friedo-oleanane triterpene", *Tetrahedron Letters*, 1983, 24(27):2799-2800.
- Kamal, et al., "Structures of two new phenolic 24-nor-D:A-friedooleananes related to zeylasterone: a partial synthesis of trimethylzeylasterone", *Tetrahedron Letters*, 1983, 24(19):2025-2028.
- Kamal, et al., "The structure of zeylasterone, the first of a new series of phenolic 24-nor-D: A friedo-oleanane triterpenes", *Tetrahedron Letters*, 1980, 21(49):4749-4752.
- Kansanen, et al., "Regulation of Nrf2-dependent gene expression by 15-deoxy-delta12,14-prostaglandin J2", *Free Radic. Biol. Med.*, 2009, 47(9): 1310-1317.
- Karin, et al., "NF- κ B in cancer: From innocent bystander to major culprit", *Nature Reviews*, 2002, 2:301-303.
- Khalid, et al., "Isolation and characterization of pristimerin as the antiparasitodal and antileishmanial agent of maytenus senegalensis (Lam.) Exell", *ARKIVOC*, 2007, 129-134.
- Klyne, et al., "The molecular rotations of polycyclic compounds. III. Polycyclic alcohols and their derivatives", *J. Chem. Soc.*, 1954, 1979-1988.

(56)

References Cited

OTHER PUBLICATIONS

- Kobayashi, et al., "The antioxidant defense system Keap1-Nrf2 comprises a multiple sensing mechanism for responding to a wide range of chemical compounds", *Mol. Cell Biol.*, 2009, 29(2):493-502.
- Kolak, et al., "Antioxidant and anticholinesterase constituents of *Salvia pocalata*", *Turkish Journal of Chemistry*, 2009, 33(6):813-823.
- Koschmieder, et al., "CDDO induces granulocytic differentiation of myeloid leukemic blasts through translational up-regulation of p42 CCAAT enhanced-binding protein alpha", *Blood*, 2007, 110(10):3695-3705.
- Kutschabsky, et al., "Natural products from Vietnamese plants. Part XV. Molecular and crystal structure of a new 24-nor triterpenoid carboxylic acid from *Acanthopanax trifoliatum*", *Croatica Chemica Acta*, 1986, 58(4):427-434.
- Lavie, et al., "Studies on epoxides. IV. Rearrangements in triterpenoids", *Tetrahedron Letters*, 1968, 17:2097-2100.
- Lavie, et al., "Tetranortriterpenoids from *Melia azadirachta*", *Chemical Communications*, 1967, 6:278-280.
- Mandel, et al., "Neuroprotective strategies in Parkinson's disease: an update on progress", *CNS Drugs*, 2003, 17(10):729-762.
- Mencherini, et al., "Triterpenoid constituents from the roots of the *Paeonia rockii* ssp. *rockii*", *J. Nat. Prod.*, 2011, 74(10):2116-2121.
- Misra, et al., "Studies of Autoxidation: Part II—Synthesis of Isomeric 2,3-diols of Δ^{12} -oleanene", *Indian Journal of Chemistry*, 1976, 14B:411-414.
- Nair, et al., "Triterpenes. XLVII. Oxidation rates of triterpenoid secondary alcohols with chromic acid", *Collection of Czechoslovak Chemical Communications*, 1976, 41(3):770-779.
- Niikura, et al., "The effects of synthetic triterpenoids on superficial zone protein synthesis in articular chondrocytes", Abstract, Orthopedic Research Society, San Diego, 2007.
- Niikura, et al., "The effects of synthetic triterpenoids on szp synthesis in articular chondrocytes", Abstract P197, Osteoarthritis and Cartilage, 2006, 14(Suppl B):S112-S113.
- Nishimura, et al., "Activity-guided isolation of triterpenoid acyl CoA cholesteryl acyl transferase (ACAT) inhibitors from *Ilex kudinchia*", *J. Nat. Prod.*, 1999, 62(7):1061-1064.
- Peakman, et al., "Characterization of 24-nor-triterpenoids occurring in sediments and crude oils by comparison with synthesized standards", *Tetrahedron*, 1991, 47(23):3779-3786.
- Ray, Denise M. et al., "The novel triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) Induces Apoptosis of Human Diffuse Large B-cell Lymphoma Cells through a Peroxisome Proliferator-activated Receptor gamma-independent Pathway", *Experimental Hematology*, 2006, 34:1201-1210.
- Ribo, et al., "Synthesis of methyl 1,11-dioxooleanan-2,12-dien-30-oate and its 24-nor derivative", *Afinidad*, 1981, 38(373):197-200.
- Rouquette, et al., "A ring-D functionalized nor-triterpenoid of the lupane series as a key intermediate in the formation of widespread hydrocarbon derivatives of higher plant origin in petroleum", *Organic Geochemistry*, 2005, 36(9):1227-1233.
- Shin, "Inhibitory roles of Nrf2 and an oleanolic triterpenoid on adipocyte differentiation and obesity", dissertation submitted to John Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy, Mar. 2009.
- Shin, et al., "Nrf2 modulates aryl hydrocarbon receptor signaling: influence on adipogenesis", *Molecular and Cellular Biology*, 2007, 27(20):7188-7197.
- Shin, et al., "Role of Nrf2 in prevention of high-fat diet-induced obesity by synthetic triterpenoid CDDO-imidazolide", *Eur. J. Pharmacol.*, 2009, 620(1-3):138-144.
- Siddiqui, et al., "Kanerin and 12,13-dihydrourosolic acid, two new pentacyclic triterpenes from the leaves of *Nerium oleander*", *J. Nat. Prod.*, 1989, 52(1):57-62.
- Slides by Reata Pharmaceuticals, "RTA 402, Therapeutic Properties III", podium presentation at BIO 2006 conference, Apr. 9-12, 2006, Chicago, Illinois.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties I", Private partnering meetings at BioSquare 2006 conference, Mar. 8-10, 2006, Geneva, Switzerland.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties II", Private partnering meetings at BIO 2006 conference, Apr. 9-12, 2006, Chicago, Illinois.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties IV", Private partnering meetings at BioPartnering Europe 2006 conference, Oct. 8-10, 2006, London, England.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties IX", Private partnering meeting at BIO Europe 2007 conference, Nov. 12-14, 2007, Hamburg, Germany.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties V", Private partnering meetings at BIO 2007 conference, May 6-9, 2007, Boston, Massachusetts.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties VI", Private partnering meetings at BIO 2007 conference, May 6-9, 2007, Boston, Massachusetts.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties VII", Podium presentation at BIO 2007 conference, May 6-9, 2007, Boston, Massachusetts.
- Slides/Handout by Reata Pharma., "RTA 402, Therapeutic Properties VIII", Private partnering meetings at BIO Europe 2007 conference, Nov. 12-14, 2007, Hamburg, Germany.
- Subba Rao, et al., "Chemical modifications of natural triterpenes—glycyrrhetic and boswellic acids: evaluation of their biological activity", *Tetrahedron*, 2008, 64:11541-11548.
- Sultana, et al., "Phytochemical studies on *Alstonia scholaris*", *Zeitschrift für Naturforschung B, A Journal of Chemical Sciences*, 2010, 65(2):203-210.
- Sun et al., "Structure-activity relationships of olean- and ursane-type triterpenoids", *Botanical Studies*, 2006, 47:339-368.
- Takaishi, et al., "Triterpenoid inhibitors of interleukin-1 secretion and tumor-promotion from *Tripterygium wilfordii* var. *regelii*", *Phytochemistry*, 1997, 45(5):969-974.
- Tanaka, et al., "A new triterpenoid from the leaves of *Eucommia ulmoides* Oliv.", *Chem. Pharm. Bull. (Tokyo)*, 1997, 45(8):1379-1380.
- Ten Haven, et al., "Early diagenetic transformation of higher-plant triterpenoids in deep-sea sediments from Baffin Bay", *Geochimica et Cosmochimica Acta*, 1992, 56(5):2001-2024.
- Ulbelen, et al., "Triterpenoids of *Salvia Horminum*, Constitution of a new diol", *Phytochemistry*, 1977, 16:790-791.
- Van Kiem, et al., "A new 24-nor-lupane-glycoside of *Acanthopanax trifoliatum*", *Arch. Pharm. Res.*, 2003, 26(9):706-708.
- Vannini, et al., "The synthetic oleanane triterpenoid, CDDO-methyl ester, is a potent antiangiogenic agent", *Molecular Cancer Therapeutics*, 2007, 6(12 Part 1):3139-3146.
- Vilayur and Harris, "Emerging therapies for chronic kidney disease: what is their role?", *Nature Reviews*, 2009, 5:375-383.
- Vincenti, et al., "The synthetic triterpenoid TP-222 inhibits RANKL induction of differentiation and MMP-9 gene expression in osteoclasts", Abstract 1385, American College of Rheumatology Annual Scientific Meeting, 2006.
- Wada and Tanaka, "Synthetic lanostane-type triterpenoids as inhibitors of DNA topoisomerase II", *Bioorganic and Medicinal Chemistry Letters*, 2005, 15(12):2966-2969.
- Waratchareeyakul, et al., "2,19-dihydroxy-3-oxo-(2,4,19)-24-nor-olean-12-en-28-oic acid monohydrate", *Acta. Cryst.*, 2007, E63, o4062-o4063.
- White, et al., "A novel demethylated oxygenated triterpenoid in crude oils from the Canadian Beaufort sea and northeast Alaska", *Tetrahedron Letters*, 1998, 39(19):3031-3034.
- You, et al., "Synthesis and cytotoxic activity of a-ring modified betulonic acid derivatives", *Bioorganic and Medicinal Chemistry Letters*, 2003, 13(19):3137-3140.
- Zhou, et al., "A new triterpenoid from the roots of *Tripterygium wilfordii*", *Chinese Chemical Letters*, 2010, 21(5):600-602.
- Ziegler, et al., "Isolation and structure of eucosterol and 16beta-hydroxyeucosterol, two novel spirocyclic nortriterpenes, and of a new 24-nor-5alpha-chola-8,16-diene-23-oic acid from bulbs of several *Eucomis* species", *Helv. Chim. Acta*, 1976, 59(6):1997-2011.

(56)

References Cited

OTHER PUBLICATIONS

Deeb, et al., "CDDO-Me Induces Apoptosis and Inhibits Akt, mTOR and NF- κ B Signaling Proteins in Prostate Cancer Cells," *Anticancer Research*, 27:3035-3044, 2007.

Office Action and Search Report in Co-pending Taiwanese Application 098113098, dated Aug. 19, 2013. (Chinese, English translation of Search Report).

Alabran, et al., "Human neuroblastoma cells rapidly enter cell cycle arrest and apoptosis following exposure to C-28 derivatives of the synthetic triterpenoid CDDO," *Cancer Biology & Therapy*, 7(5):709-717, 2008.

Chadalapaka, et al., "Structure-dependent inhibition of bladder and pancreatic cancer cell growth by 2-substituted glycyrrhetic and ursolic acid derivatives," *Bioorganic & Medicinal Chemistry Letters*, 18:2633-2639, 2008.

Deeb, et al., "CDDO-Me inhibits proliferation, induces apoptosis, down-regulates Akt, mTOR, NF- κ B and NF- κ B-regulated antiapoptotic and proangiogenic proteins in TRAMP prostate cancer cells," *J. of Experimental Therapeutics and Oncology*, 7:31-39, 2008.

Heather E. Ferguson, "PPAR γ ligands have potent anti-fibrotic activity: mechanism of action and implications for therapy of pulmonary fibrosis," Dissertation, University of Rochester, 2008.

Govindachari, et al., "Gymnosporol, a new pentacyclic triterpene from *Gymnosporia rothiana* Laws," *Indian J. of Chem.*, 8:395-397, 1970.

Hughes, et al., "The synthetic triterpenoid CDDO-Im inhibits fatty acid synthase expression and has antiproliferative and proapoptotic effects in human liposarcoma cells," *Cancer Investigation*, 26:118-127, 2008.

Hyer, et al., "Apoptotic activity and mechanism of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid and related synthetic triterpenoids in prostate cancer," *Cancer Res.*, 68:2927-2933, 2008.

Liu, et al., "Coordinate regulation of enzyme markers for inflammation and for protection against oxidants and electrophiles," *Proc. Natl. Acad. Sci.*, 105(41):15926-15931, 2008.

Andrew E. Place, "Pre-clinical evaluation of the novel synthetic triterpenoid CDDO-Imidazolide," Thesis, Dartmouth College, May 5, 2004.

Pradhan and De, "Preparation of triterpenoid diosphenol via oximinoketone & structure of baccatin," *Indian J. of Chem.*, 21B:823-828, 1982.

Riccioni, et al., "Resistance of acute myeloid leukemic cells to the triterpenoid CDDO-Imidazolide is associated with low caspase-8 and FADD levels," *Leukemia Research*, 32:1244-1258, 2008.

Samudio, et al., "Inhibition of mitochondrial metabolism by methyl-2-cyano-3,12-dioxoolean-1,9-diene-28-oate induces apoptotic or autophagic cell death in chronic myelogenous leukemia cells," *Mol. Cancer Ther.*, 7(5):1130-1139, 2008.

Subba Rao, et al., "Chemical modifications of natural triterpenes—glycyrrhetic and boswellic acids: evaluation of their biological activity," *Tetrahedron*, 64(51):11541-11548, 2008.

Sun, et al., "Therapeutic potential of synthetic triterpenoids in neuroblastoma," *Cancer Biology & Therapy*, 7(5):720-722, 2008.

To, et al., "The synthetic triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid-imidazolide alters transforming growth factor β -dependent signaling and cell migration by affecting the cytoskeleton and the polarity complex," *J. Biol. Chem.*, 283:11700-11713, 2008.

Venè, et al., "Glycogen synthase kinase 3 β regulates cell death induced by synthetic triterpenoids," *Cancer Res.*, 68:6987-6996, 2008.

Wang, "Differentiating and anti-inflammatory activities of the triterpenoid, CDDO," Thesis, Dartmouth College, May 4, 2001.

Wen, et al., "Naturally occurring pentacyclic triterpenes as inhibitors of glycogen phosphorylase: synthesis, structure-activity relationships, and X-ray crystallographic studies," *J. Med. Chem.*, 51:3540-3554, 2008.

Xu, et al., "Inhibition of the signal transducer and activator of transcription-3 (STAT3) signaling pathway by 4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylic acid esters," *J. Med. Chem.*, 51:4115-4121, 2008.

Zou, et al., "c-FLIP downregulation contributes to apoptosis induction by the novel synthetic triterpenoid methyl-2-cyano-3,12-dioxoolean-1,9-dien-28-oate (CDDO-Me) in human lung cancer cells," *Cancer Biology & Therapy*, 6(10):1614-1620, 2007.

Zou, et al., "Coupling of endoplasmic reticulum stress to CDDO-Me-induced up-regulation of death receptor 5 via a CHOP-dependent mechanism involving JNK activation," *Cancer Res.*, 68:7484-7492, 2008.

* cited by examiner

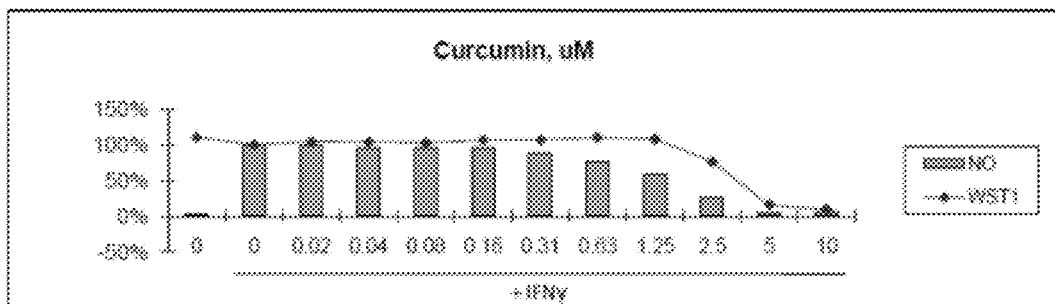


FIG. 1

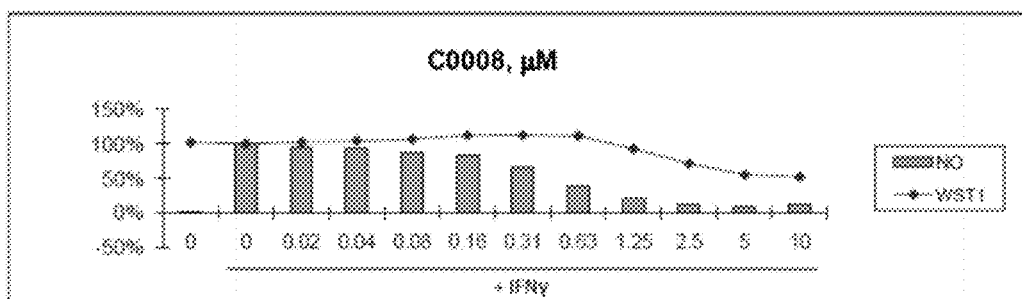


FIG. 2

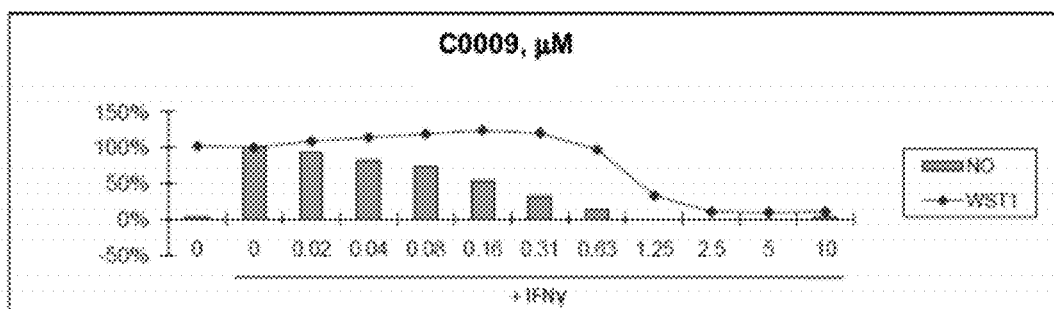


FIG. 3

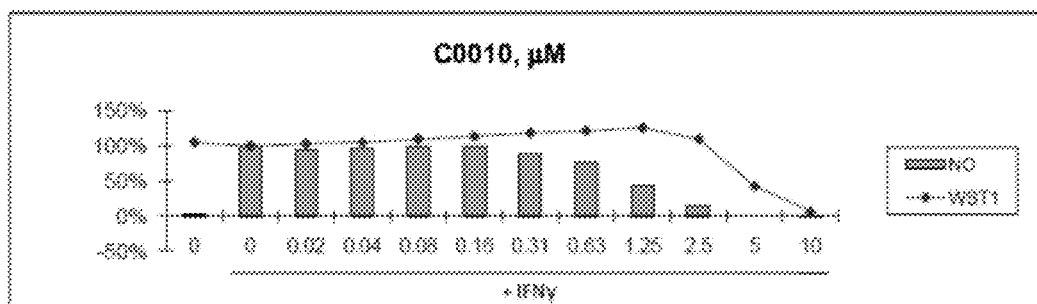


FIG. 4

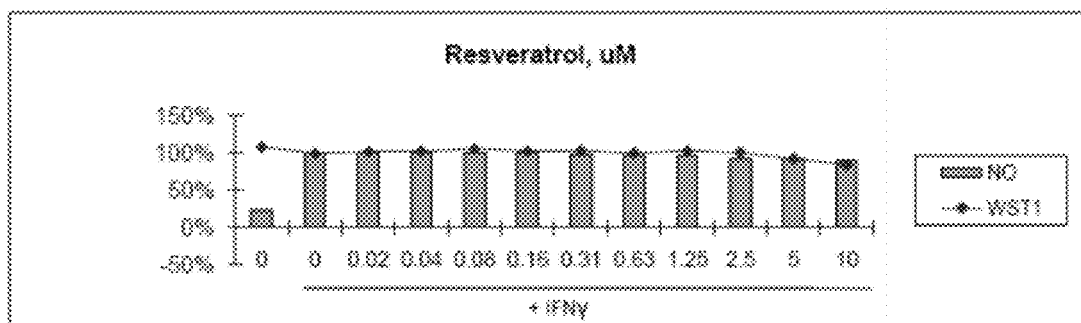


FIG. 5

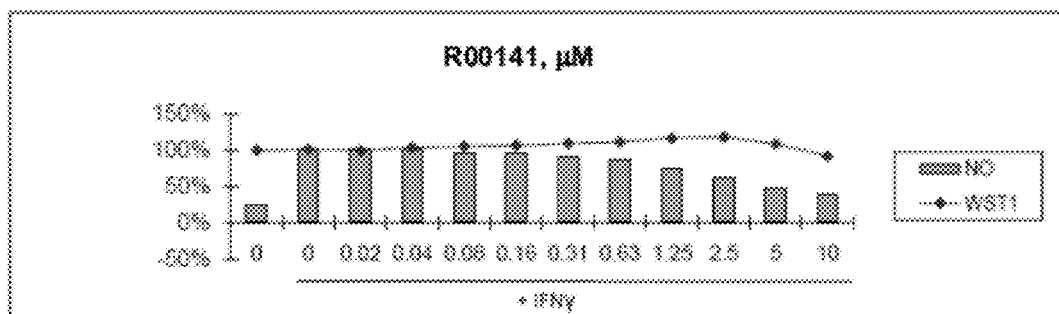


FIG. 6

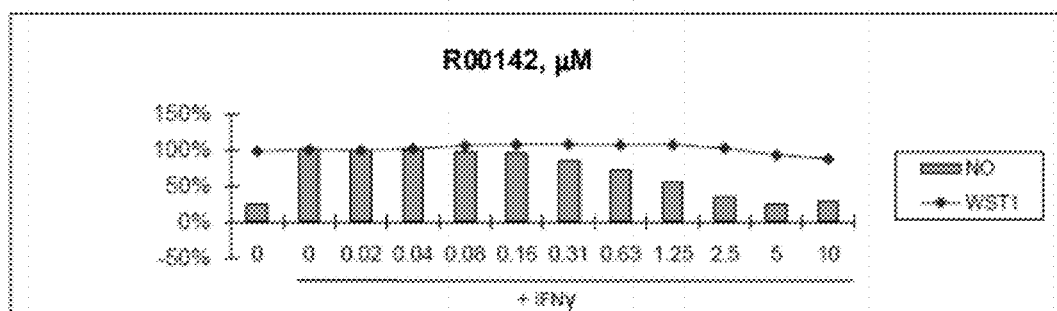


FIG. 7

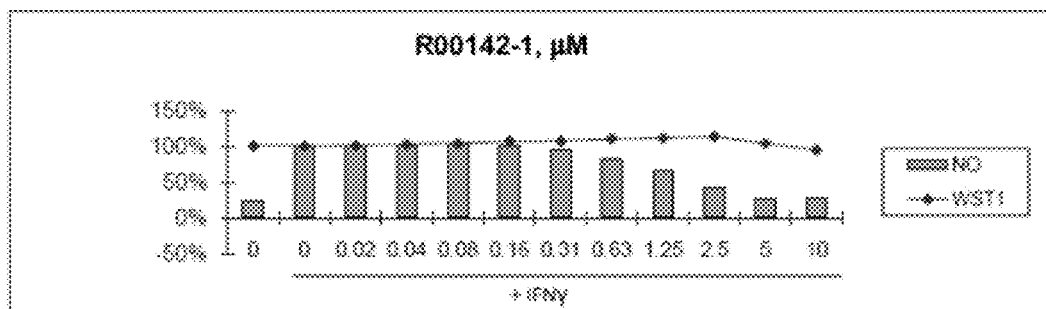


FIG. 8

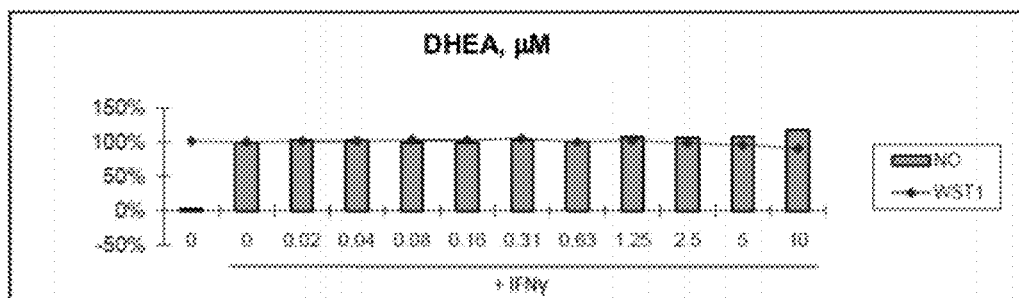


FIG. 9

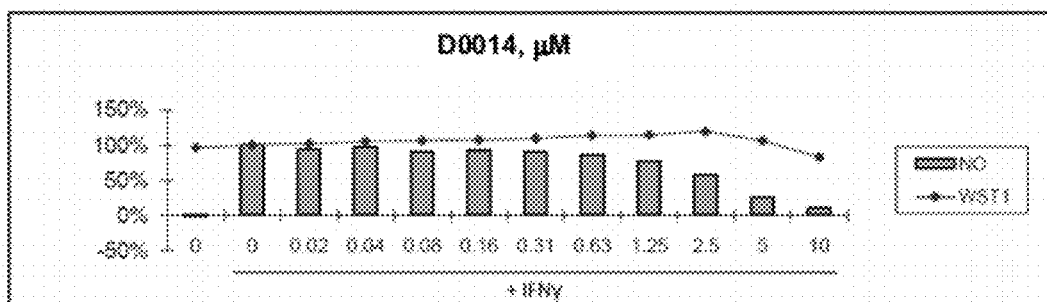


FIG. 10

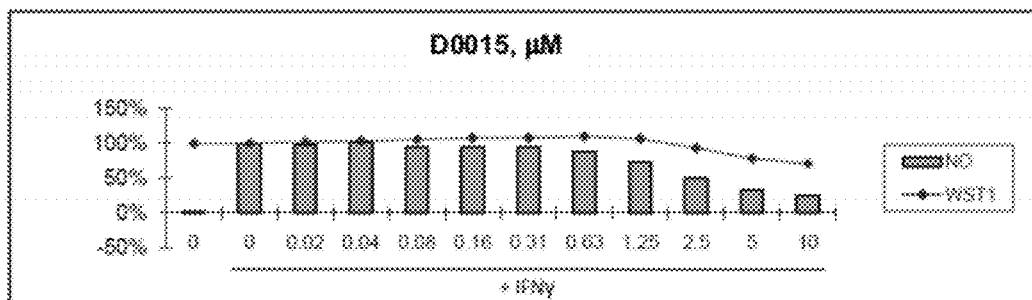


FIG. 11

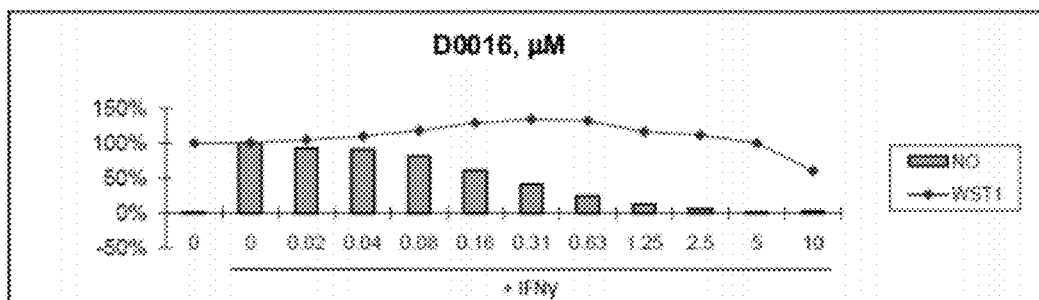


FIG. 12

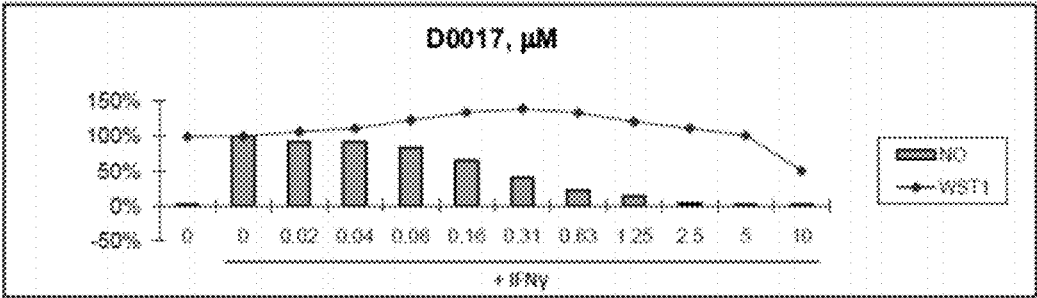


FIG. 13

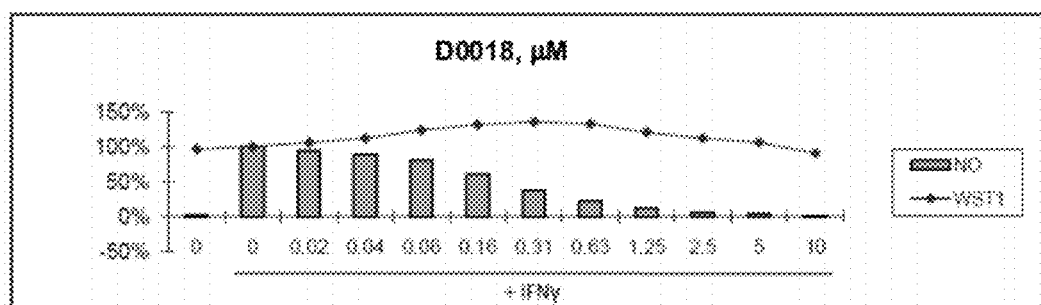


FIG. 14

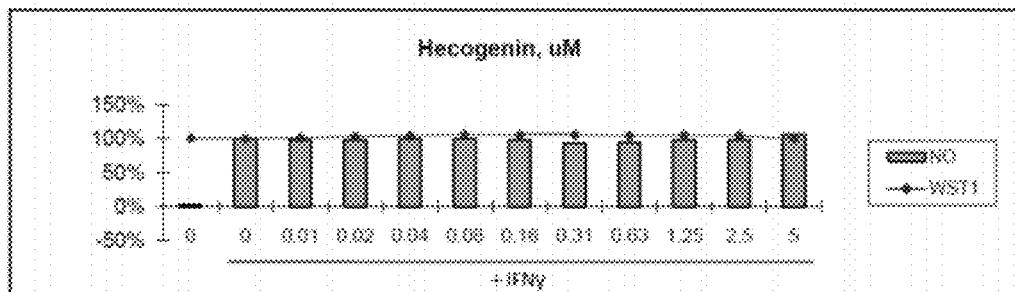


FIG. 15

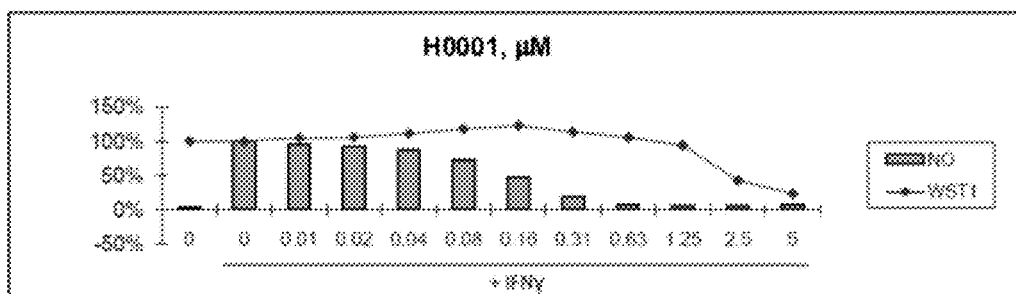


FIG. 16

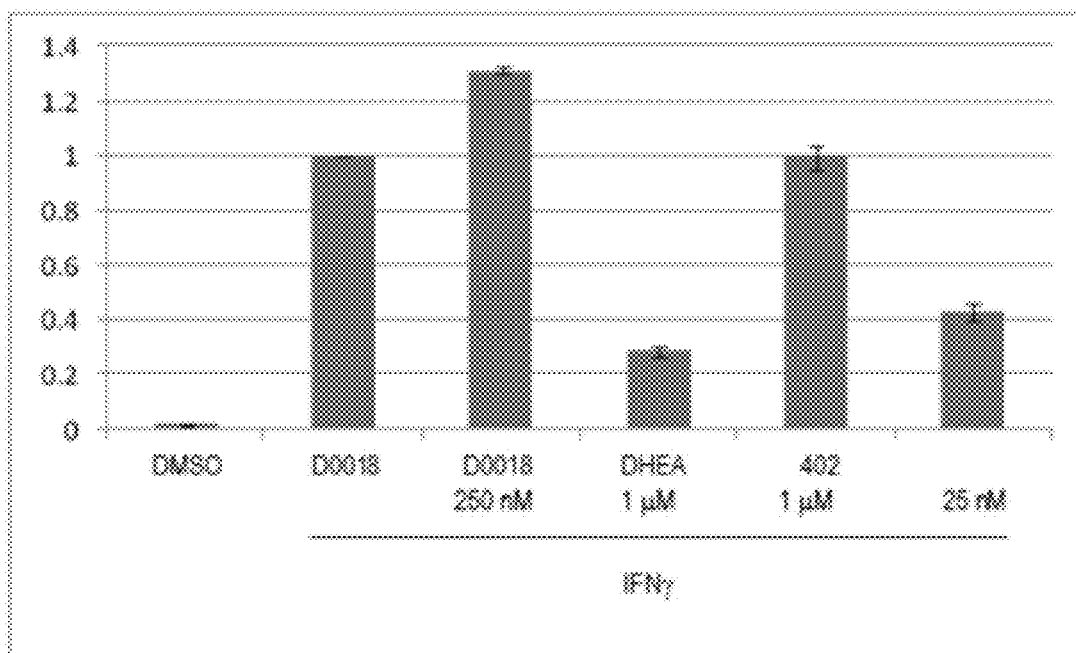


FIG. 17

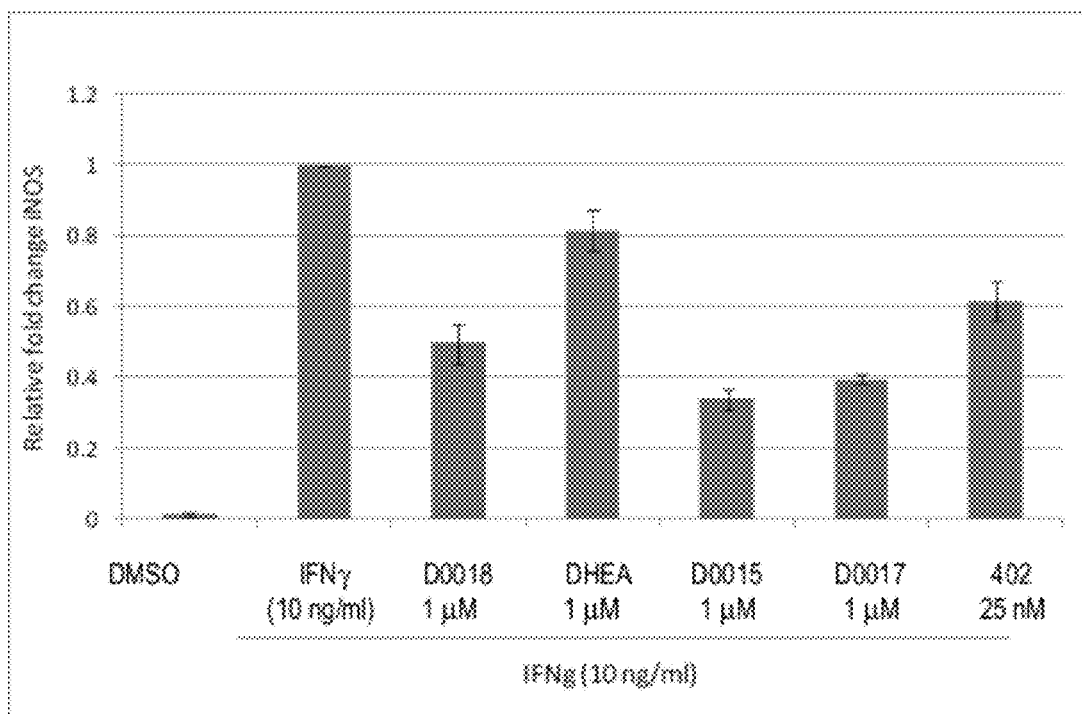


FIG. 18

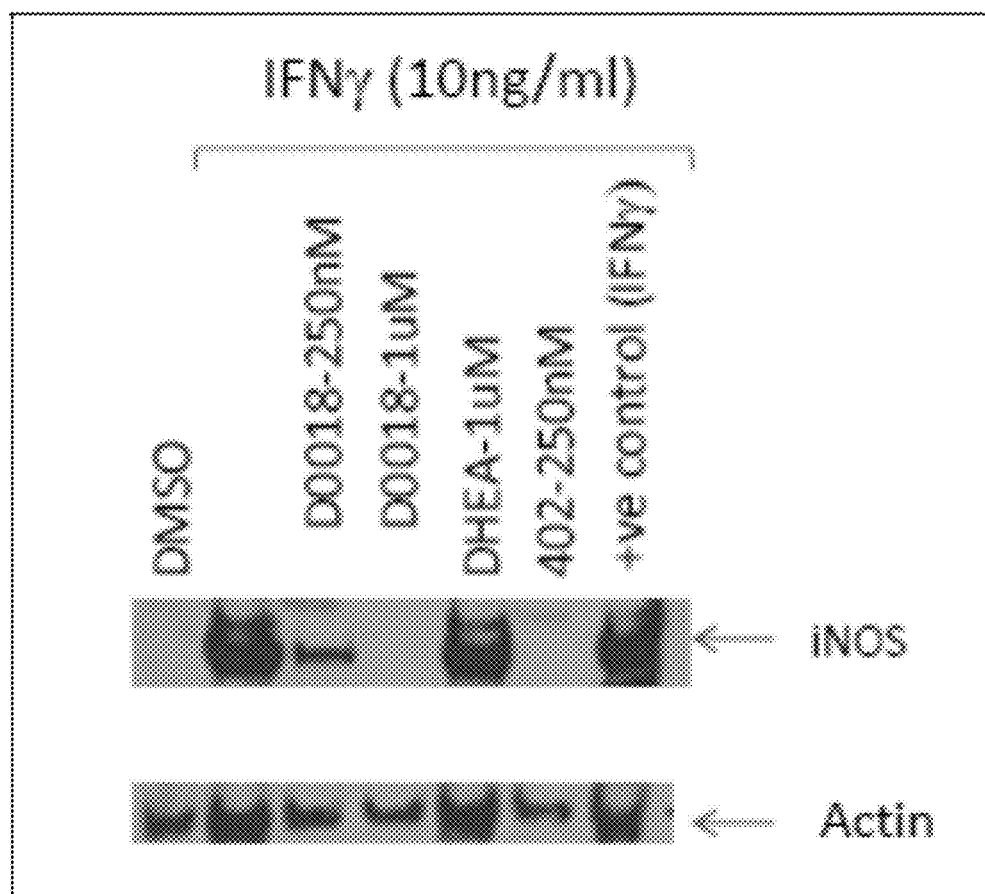


FIG. 19

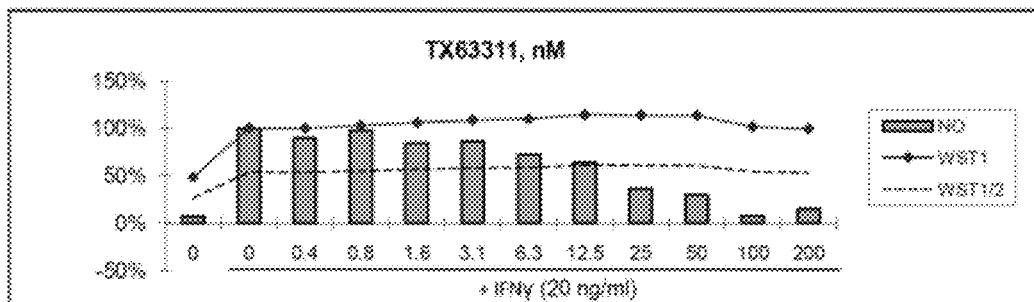


FIG. 20

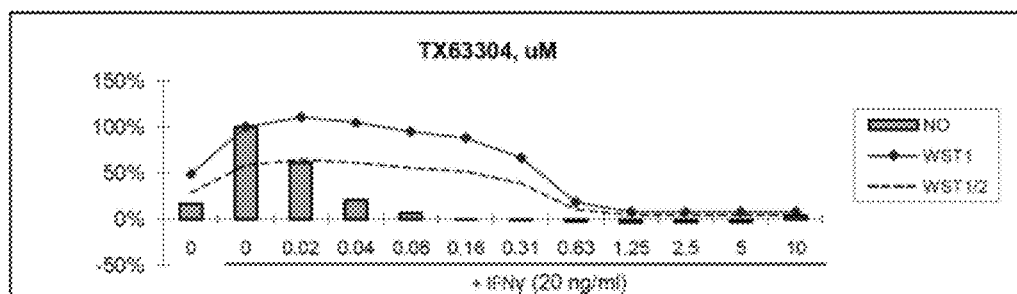


FIG. 21

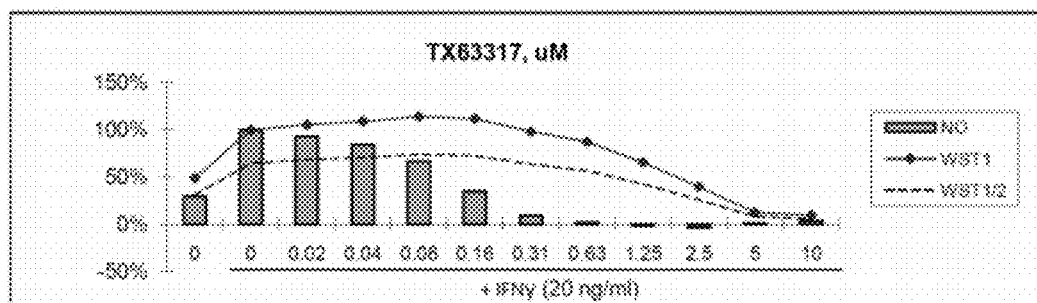


FIG. 22

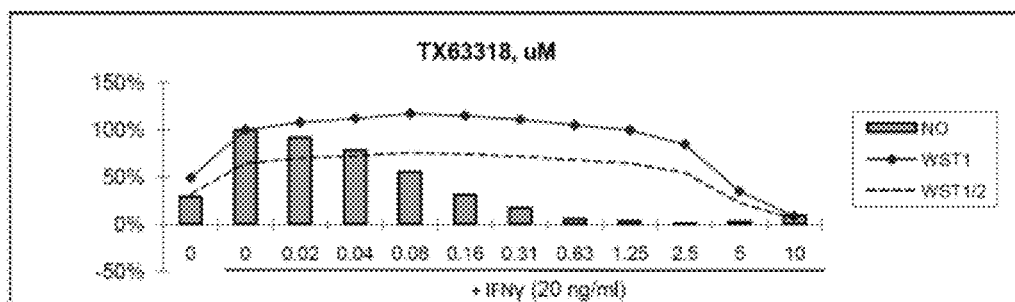


FIG. 23

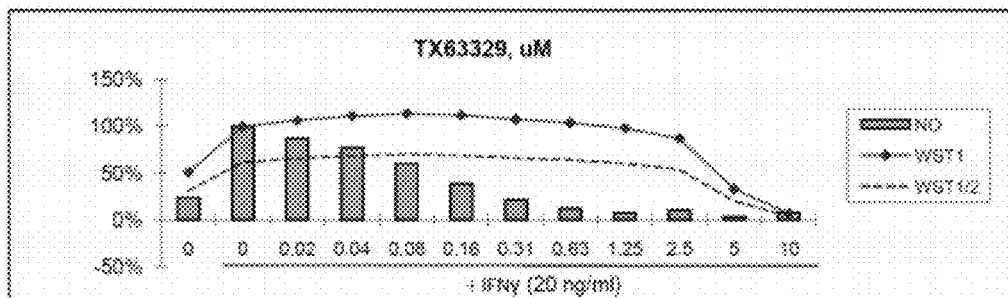


FIG. 24

1

NATURAL PRODUCT ANALOGS INCLUDING AN ANTI-INFLAMMATORY CYANOENONE PHARMACORE AND METHODS OF USE

The present application is a continuation application of U.S. patent application Ser. No. 12/426,889 filed Apr. 20, 2009, which claims the benefit of priority to U.S. Provisional Application No. 61/046,363, filed Apr. 18, 2008, the entire contents of each of which are incorporated herein by reference in their entirety without disclaimer.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of biology and medicine. More particularly, it concerns compounds and methods for the treatment and prevention of diseases such as those associated with oxidative stress and inflammation.

II. Description of Related Art

Many serious and intractable human diseases are associated with dysregulation of inflammatory processes, including diseases such as cancer, atherosclerosis, and diabetes, which were not traditionally viewed as inflammatory conditions. Similarly, autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis, and multiple sclerosis involve inappropriate and chronic activation of inflammatory processes in affected tissues, arising from dysfunction of self vs. non-self recognition and response mechanisms in the immune system. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neural damage is correlated with activation of microglia and elevated levels of pro-inflammatory proteins such as inducible nitric oxide synthase (iNOS).

One aspect of inflammation is the production of inflammatory prostaglandins such as prostaglandin E₂, whose precursors are produced by COX-2. High levels of COX-2 are found in inflamed tissues. Consequently, inhibition of COX-2 is known to reduce many symptoms of inflammation and a number of important anti-inflammatory drugs (e.g., ibuprofen and celecoxib) act by inhibiting COX-2 activity. Recent research, however, has demonstrated that a class of cyclopentenone prostaglandins (e.g., 15-deoxy prostaglandin J₂, a.k.a. PGJ₂) plays a role in stimulating the orchestrated resolution of inflammation. COX-2 is also associated with the production of cyclopentenone prostaglandins. Consequently, inhibition of COX-2 may interfere with the full resolution of inflammation, potentially promoting the persistence of activated immune cells in tissues and leading to chronic, "smoldering" inflammation. This effect may be responsible for the increased incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long periods of time. Corticosteroids, another important class of anti-inflammatory drugs, have many undesirable side effects and frequently are not suitable for chronic use. Newer protein-based drugs, such as anti-TNF monoclonal antibodies, have proven to be effective for the treatment of certain autoimmune diseases such as rheumatoid arthritis. However, these compounds must be administered by injection, are not effective in all patients, and may have severe side effects. In many severe forms of inflammation (e.g., sepsis, acute pancreatitis), existing drugs are ineffective. In addition, currently available drugs do not have significant antioxidant properties, and are not effective in reducing oxidative stress associated with excessive production of reactive oxygen species and related molecules such as peroxynitrite. Accordingly, there is a pressing need for improved therapeutics with antioxidant and anti-inflammatory properties.

2

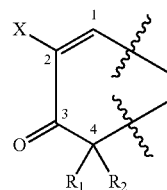
Synthetic triterpenoid analogs of oleanolic acid have been shown to be inhibitors of cellular inflammatory processes, such as the induction by IFN- γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda et al. (2000a); Honda et al. (2000b), and Honda et al. (2002), which are all incorporated herein by reference. For example, one of these, 2-cyano-3,12-dioxooleane-1,9(11)-dien-28-oic acid methyl ester (CDDO-Me), is currently in clinical trials for a variety of disorders related to inflammation, including cancer and diabetic nephropathy. Synthetic derivatives of another triterpenoid, betulinic acid, have also been shown to inhibit cellular inflammatory processes, although these compounds have been less extensively characterized (Honda et al., *Bioorg Med Chem Lett.* 2006; 16(24): 6306-9). The pharmacology of these synthetic triterpenoid molecules is complex. Compounds derived from oleanolic acid have been shown to affect the function of multiple protein targets and thereby modulate the activity of several important cellular signaling pathways related to oxidative stress, cell cycle control, and inflammation (e.g., Dinkova-Kostova et al., *Proc Natl Acad Sci USA.* 2005; 102(12):4584-9; Ahmad et al., *J. Biol Chem.* 2006; 281(47):35764-9; Ahmad et al., *Cancer Res.* 2008; 68(8):2920-6; Liby et al., *Nat Rev Cancer.* 2007; 7(5):357-69). Derivatives of betulinic acid, though they have shown comparable anti-inflammatory properties, also appear to have significant differences in their pharmacology compared to OA-derived compounds (Liby et al., *Mol Cancer Ther* 2007; 6(7)). Further, it is not certain that the triterpenoid starting materials employed to date have optimal properties compared to other possible starting materials. Given that the biological activity profiles of known triterpenoid derivatives vary, and in view of the wide variety of diseases that may be treated or prevented with compounds having potent antioxidant and anti-inflammatory effects, and the high degree of unmet medical need represented within this variety of diseases, it is desirable to synthesize new compounds with diverse structures that may have improved biological activity profiles for the treatment of one or more indications.

SUMMARY OF THE INVENTION

The present disclosure overcomes limitation of the prior art by providing new compounds with antioxidant and anti-inflammatory properties, methods for their manufacture, and methods for their use.

In some aspects, the disclosure provides compounds comprising:

- a) the basic skeleton of an organic compound having two to eight five and/or six-membered rings provided that the basic skeleton is not the basic skeleton of argentin, betulinic acid, lanostane, oleanic acid, boswellic acid, glycyrrhetic acid, ursolic acid, or tricyclic-bis-enone;
- b) a structural unit of the formula:



wherein:

the carbon atoms labeled 1, 2 and 3 are part of a five or six-membered ring;

X is cyano or —C(O)R_a , wherein R_a is:

hydrogen, hydroxy, halo, amino, hydroxyamino, azido or mercapto; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12), amido_(C≤12), alkylsilyloxy_(C≤12), or substituted versions of any of these groups; and

R_1 and R_2 are each independently:

hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups; or

R_1 and R_2 are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12); and

c) from 0 to 8 chemical groups attached to a carbon atom of the basic skeleton other than carbon atoms 1, 2, 3 or 4, wherein each chemical group is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12), amido_(C≤12), alkylimino_(C≤12), alkenylimino_(C≤12), alkynylimino_(C≤12), arylimino_(C≤12), aralkylimino_(C≤12), heteroarylimino_(C≤12), heteroaralkylimino_(C≤12), acylimino_(C≤12), alkylthio_(C≤12), alkenylthio_(C≤12), alkynylthio_(C≤12), arylthio_(C≤12), aralkylthio_(C≤12), heteroarylthio_(C≤12), heteroaralkylthio_(C≤12), acylthio_(C≤12), thioacyl_(C≤12), alkylsulfonyl_(C≤12), alkenylsulfonyl_(C≤12), alkynylsulfonyl_(C≤12), arylsulfonyl_(C≤12), aralkylsulfonyl_(C≤12), heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12), alkylammonium_(C≤12), alkylsulfonium_(C≤12), alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted version of any of these groups;

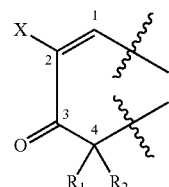
or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, acetals, ketals, prodrugs, or optical isomers thereof.

In some embodiments, R_1 and R_2 are each independently hydrogen, alkyl_(C≤8) or substituted alkyl_(C≤8). In some embodiments, R_1 and R_2 are both hydrogen. In some embodiments, R_1 and R_2 are both methyl. In some embodiments, R_1

and R_2 are both not hydrogen. In some embodiments, the organic compound is not a triterpenoid.

In some aspects, the disclosure provides compounds comprising:

- a) the basic skeleton of a natural product having two to eight rings, provided that the natural product is not argentatin, betulinic acid, lanostane, oleanic acid, or ursolic acid;
- b) a structural unit of the formula:



wherein:

the carbon atoms labeled 1, 2 and 3 are part of a six-membered ring;

X is cyano, fluoroalkyl_(C≤8), substituted, fluoroalkyl_(C≤8), or —C(O)R_a wherein R_a is:

hydrogen, hydroxy, halo, amino, hydroxyamino, azido or mercapto; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12), amido_(C≤12), alkylsilyloxy_(C≤12), or substituted versions of any of these groups; and

R_1 and R_2 are each independently:

hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups; or

R_1 and R_2 are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12); and

c) from 0 to 8 chemical groups attached to a carbon atom of the basic skeleton other than carbon atoms 1, 2, 3 or 4, wherein each chemical group is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12)

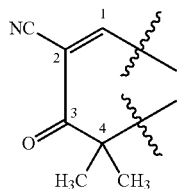
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amido_(C≤12), alkylimino_(C≤12), alkenylimino_(C≤12),
alkynylimino_(C≤12), arylimino_(C≤12),
aralkylimino_(C≤12), heteroarylimino_(C≤12), het-
eroaralkylimino_(C≤12), acylimino_(C≤12), alkylthio_(C≤12),
alkenylthio_(C≤12), alkynylthio_(C≤12), arylthio_(C≤12),
aralkylthio_(C≤12), heteroarylthio_(C≤12), heteroaralkylthio_(C≤12),
acylthio_(C≤12), thioacyl_(C≤12),
alkylsulfonyl_(C≤12), alkenylsulfonyl_(C≤12), alkynylsul-
fonyl_(C≤12), arylsulfonyl_(C≤12), aralkylsulfonyl_(C≤12),
heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12),
alkyl-ammonium_(C≤12), alkylsulfonium_(C≤12),
alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted ver-
sion of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, sol-
vates, tautomers, acetals, ketals, prodrugs, or optical isomers
thereof.

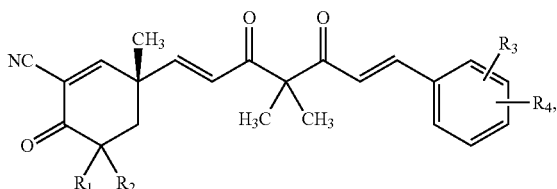
In some embodiments, R₁ and R₂ are each independently
hydrogen, alkyl_(C≤8) or substituted alkyl_(C≤8). In some
embodiments, R₁ and R₂ are both hydrogen. In some embodi-
ments, R₁ and R₂ are both methyl. In some embodiments, R₁
and R₂ are both not hydrogen. In some embodiments, the
natural product is not boswellic acid or glycyrrhetic acid. In
some embodiments, the natural product is not a triterpenoid.
In some embodiments, X is —CN or —C(=O)NHS(=O)₂
CH₃. In some embodiments, X is —CN. In some embodi-
ments, X is fluoroalkyl_(C≤8). In some embodiments, X is
—CF₃.

In some embodiments, the structural unit is further defined
as:



In some embodiments, the basic skeleton of the natural
product has two rings. In some embodiments, the rings are
connected to one another by a single chain of atoms. In some
embodiments, the backbone of the single chain further com-
prises at least one carbon-carbon double bond.

In some embodiments, the natural product is curcumin. In
some embodiments, the compound is further defined by the
formula:



wherein:

R₁ and R₂ are each independently:

hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12),
aralkoxy_(C≤12), heteroaryloxy_(C≤12),
heteroaralkoxy_(C≤12), acyloxy_(C≤12),

6

alkylamino_(C≤12), dialkylamino_(C≤12),
arylamino_(C≤12), aralkylamino_(C≤12), heteroarylami-
no_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), or a
substituted version of any of these groups; or

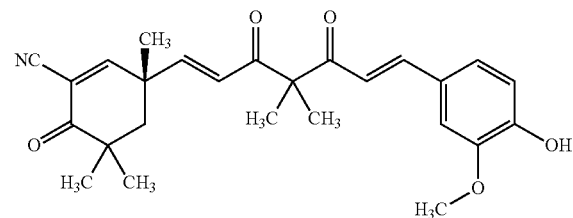
R₁ and R₂ are taken together and are alkanediyl_(C≤12), alk-
enediyl_(C≤12), alkanediyl_(C≤12); or alkenediyl_(C≤12); and
R₃ and R₄ are each independently:

hydrogen, hydroxy, halo, amino, hydroxyamino, nitro,
cyano, azido, or mercapto; or

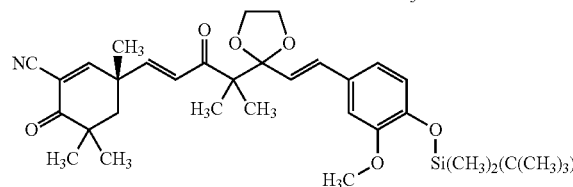
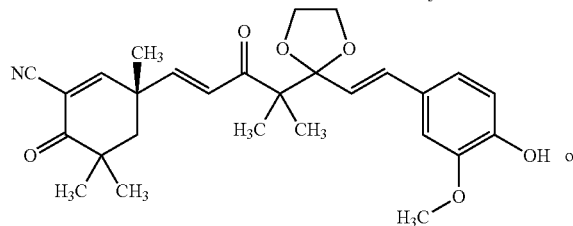
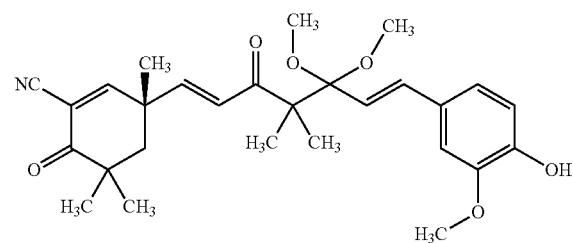
alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
acyl_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyl-
oxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroary-
loxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkyl-
lamino_(C≤12), dialkylamino_(C≤12),
alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylami-
no_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), het-
eroarylamino_(C≤12), heteroaralkylamino_(C≤12),
amido_(C≤12), alkylsulfonamino_(C≤12),
alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted
version of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, sol-
vates, tautomers, acetals, ketals, prodrugs, or optical isomers
thereof. In some variations, R₁ and R₂ are both methyl.

For example, the disclosure provides:



or pharmaceutically acceptable salts, hydrates, solvates, tau-
tomers, or optical isomers thereof. For example, the disclo-
sure provides:

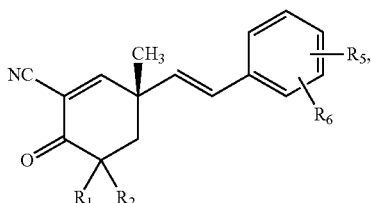


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or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

In some embodiments, the natural product is resveratrol. In some embodiments, the compound is further defined by the formula:



wherein:

R₁ and R₂ are each independently:

hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups; or

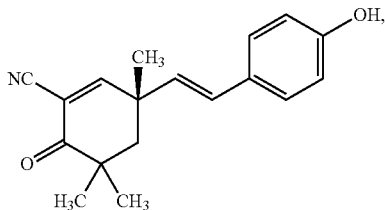
R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12); and

R₅ and R₆ are each independently:

hydrogen, hydroxy, halo, amino, hydroxyamino, nitro, cyano, azido, or mercapto; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted version of any of these groups;

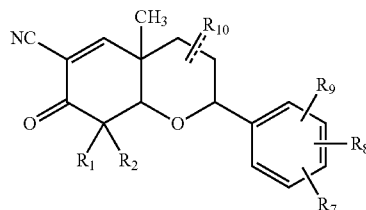
or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, acetals, ketals, prodrugs, or optical isomers thereof. In some embodiments, R₁ and R₂ are both methyl. For example, the disclosure provides:



or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

In some embodiments, the basic skeleton of the natural product has three rings. In some embodiments, the natural product is gallic catechol. In some embodiments, the compound is further defined by the formula:

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wherein:

R₁ and R₂ are each independently:

hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups; or

R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12);

R₇, R₈ and R₉ are each independently:

hydrogen, hydroxy, halo, amino, hydroxyamino, nitro, cyano, azido, or mercapto; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroaryl-heteroaralkylamino_(C≤12), amido_(C≤12), alkylsilyl_(C≤12), amino_(C≤12), alkylsilyloxy_(C≤12), or a substituted version of any of these groups; and

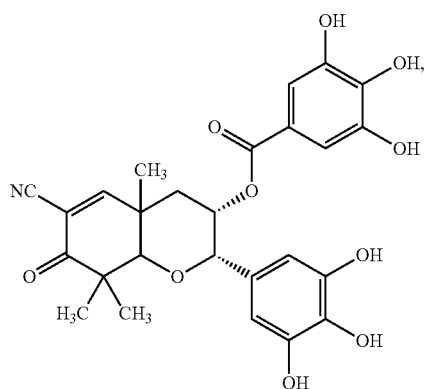
R₁₀ is:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12), amido_(C≤12), alkylimino_(C≤12), alkenylimino_(C≤12), alkynylimino_(C≤12), arylimino_(C≤12), aralkylimino_(C≤12), heteroarylimino_(C≤12), heteroaralkylimino_(C≤12), acylimino_(C≤12), alkylthio_(C≤12), alkenylthio_(C≤12), alkynylthio_(C≤12), arylthio_(C≤12), aralkylthio_(C≤12), heteroarylthio_(C≤12), heteroaralkylthio_(C≤12), acylthio_(C≤12), thioacyl_(C≤12), alkylsulfonyl_(C≤12), alkenylsulfonyl_(C≤12), alkynylsulfonyl_(C≤12), arylsulfonyl_(C≤12), aralkylsulfonyl_(C≤12), heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12), alkyl-ammonium_(C≤12), alkylsulfonium_(C≤12), alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted version of any of these groups;

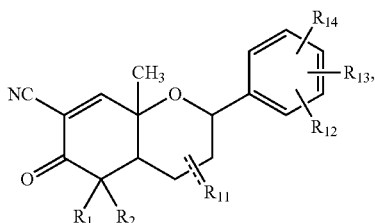
or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, acetals, ketals, prodrugs, or optical isomers thereof. In some embodiments, R₁ and R₂ are both methyl. For example, the disclosure provides:

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or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

In some embodiments, the compound is further defined by the formula:



wherein:

R₁ and R₂ are each independently:

hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12),
aralkoxy_(C≤12), heteroaryloxy_(C≤12),
heteroaralkoxy_(C≤12), acyloxy_(C≤12),
alkylamino_(C≤12), dialkylamino_(C≤12),
arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12),
heteroaralkylamino_(C≤12), amido_(C≤12), or a
substituted version of any of these groups; or

R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12);

R₁₁ is:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12),
alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12),
aralkoxy_(C≤12), heteroaryloxy_(C≤12),
heteroaralkoxy_(C≤12), acyloxy_(C≤12),
alkylamino_(C≤12), dialkylamino_(C≤12),
alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12),
arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12),
heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12),
alkenylimino_(C≤12), alkynylimino_(C≤12),
arylimino_(C≤12), aralkylimino_(C≤12),
heteroarylimino_(C≤12), heteroaralkylimino_(C≤12),
acylimino_(C≤12), alkylthio_(C≤12), alkenylthio_(C≤12),
alkynylthio_(C≤12), arylthio_(C≤12), aralkylthio_(C≤12),
heteroarylthio_(C≤12), heteroaralkylthio_(C≤12),
acylthio_(C≤12), thioacyl_(C≤12), alkylsulfonyl_(C≤12),
alkenylsulfonyl_(C≤12), alkynylsulfonyl_(C≤12), arylsul-

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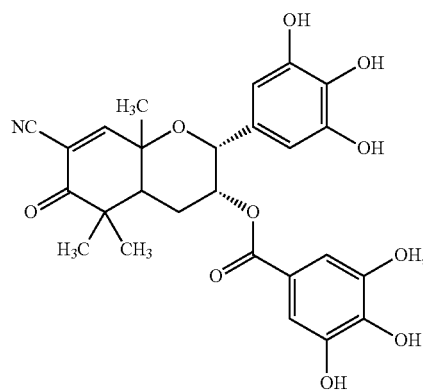
fonyl_(C≤12), aralkylsulfonyl_(C≤12),
heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12),
alkyl-ammonium_(C≤12), alkylsulfonium_(C≤12), alkyl-
silyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted ver-
sion of any of these groups; and

R₁₂, R₁₃ and R₁₄ are each independently:

hydrogen, hydroxy, halo, amino, hydroxyamino, nitro, cyano, azido, or mercapto; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
acyl_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12),
aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12),
heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12),
dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12),
alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12),
heteroarylamino_(C≤12), heteroaralkylamino_(C≤12),
amido_(C≤12), alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a
substituted version of any of these groups;

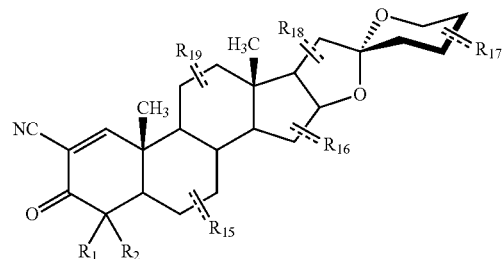
or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, acetals, ketals, prodrugs, or optical isomers thereof. In some embodiments, R₁ and R₂ are both methyl. For example, the disclosure provides:



or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

In some embodiments, the basic skeleton of the natural product has four rings. In other embodiments, the basic skeleton of the natural product has five rings. In some embodiments, the natural product is celastrol. In further embodiments, the basic skeleton of the natural product has six rings. In some embodiments, the natural product is hecogenin, tigogenin, or sarsapogenin.

In some embodiments, the compound is further defined by the formula:



wherein:

R₁ and R₂ are each independently:

hydrogen; or

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alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
 aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
 acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12),
 aralkoxy_(C≤12), heteroaryloxy_(C≤12),
 heteroaralkoxy_(C≤12), acyloxy_(C≤12),
 alkylamino_(C≤12), dialkylamino_(C≤12),
 arylamino_(C≤12), aralkylamino_(C≤12), heteroarylami-
 no_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), or a
 substituted version of any of these groups; or

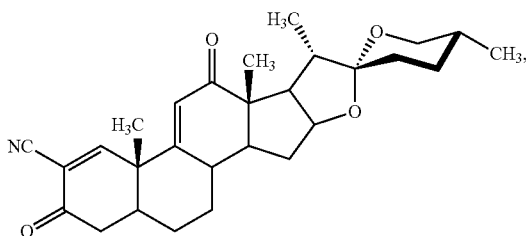
R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12); and

R₁₅, R₁₆, R₁₇, R₁₈ and R₁₉ are each independently:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

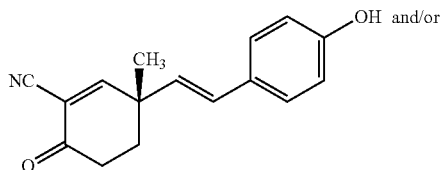
alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
 aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
 acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12),
 alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12),
 aralkoxy_(C≤12), heteroaryloxy_(C≤12),
 heteroaralkoxy_(C≤12), acyloxy_(C≤12),
 alkoxyamino_(C≤12), alkylamino_(C≤12),
 dialkylamino_(C≤12), alkenylamino_(C≤12), alkynylami-
 no_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), het-
 eroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkyl-
 sulfonylamino_(C≤12), amido_(C≤12), alkylimino_(C≤12),
 alkenylimino_(C≤12), alkynylimino_(C≤12),
 arylimino_(C≤12), aralkylimino_(C≤12),
 heteroarylimino_(C≤12), heteroaralkylimino_(C≤12),
 acylimino_(C≤12), alkylthio_(C≤12), alkenylthio_(C≤12),
 alkynylthio_(C≤12), arylthio_(C≤12), aralkylthio_(C≤12),
 heteroarylthio_(C≤12), heteroaralkylthio_(C≤12),
 acylthio_(C≤12), thioacyl_(C≤12), alkylsulfonyl_(C≤12),
 alkenylsulfonyl_(C≤12), alkynylsulfonyl_(C≤12), arylsul-
 fonyl_(C≤12), aralkylsulfonyl_(C≤12),
 heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12),
 alkyl-ammonium_(C≤12), alkylsulfonium_(C≤12), alkyl-
 silyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted ver-
 sion of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, sol-
 vates, tautomers, acetals, ketals, prodrugs, or optical isomers
 thereof. In some embodiments, R₁ and R₂ are both methyl. In
 some embodiments, R₁₇ is methyl. For example, the disclo-
 sure provides:



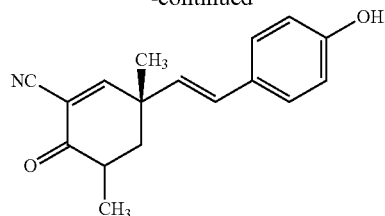
or pharmaceutically acceptable salts, hydrates, solvates, tau-
 tomers, or optical isomers thereof.

In some embodiments, the disclosure provides:



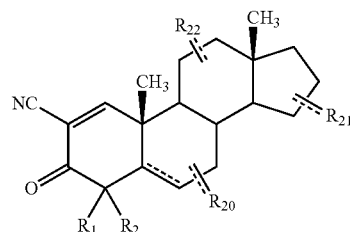
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or pharmaceutically acceptable salts, hydrates, solvates, tau-
 tomers, or optical isomers thereof.

In another aspect, the disclosure provides compounds of
 the formula:



wherein:

R₁ and R₂ are each independently:

hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
 aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
 acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12),
 aralkoxy_(C≤12), heteroaryloxy_(C≤12),
 heteroaralkoxy_(C≤12), acyloxy_(C≤12),
 alkylamino_(C≤12), dialkylamino_(C≤12),
 arylamino_(C≤12), aralkylamino_(C≤12), heteroarylami-
 no_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), or a
 substituted version of any of these groups; or

R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12); and

R₂₀, R₂₁, and R₂₂ are each independently:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

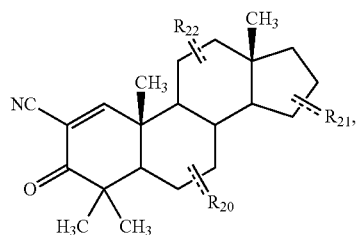
alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
 aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),
 acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12),
 alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12),
 aralkoxy_(C≤12), heteroaryloxy_(C≤12),
 heteroaralkoxy_(C≤12), acyloxy_(C≤12),
 alkoxyamino_(C≤12), alkylamino_(C≤12),
 dialkylamino_(C≤12), alkenylamino_(C≤12), alkynylami-
 no_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), het-
 eroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkyl-
 sulfonylamino_(C≤12), amido_(C≤12), alkylimino_(C≤12),
 alkenylimino_(C≤12), alkynylimino_(C≤12),
 arylimino_(C≤12), aralkylimino_(C≤12),
 heteroarylimino_(C≤12), heteroaralkylimino_(C≤12),
 acylimino_(C≤12), alkylthio_(C≤12), alkenylthio_(C≤12),
 alkynylthio_(C≤12), arylthio_(C≤12), aralkylthio_(C≤12),
 heteroarylthio_(C≤12), heteroaralkylthio_(C≤12),
 acylthio_(C≤12), thioacyl_(C≤12), alkylsulfonyl_(C≤12),
 alkenylsulfonyl_(C≤12), alkynylsulfonyl_(C≤12), arylsul-
 fonyl_(C≤12), aralkylsulfonyl_(C≤12),
 heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12),
 alkyl-ammonium_(C≤12), alkylsulfonium_(C≤12), alkyl-
 silyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted ver-
 sion of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, sol-
 vates, tautomers, acetals, ketals, prodrugs, or optical isomers

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thereof. In some embodiments, R_1 and R_2 are both hydrogen. In other embodiments, R_1 and R_2 are not hydrogen. In still other embodiments, R_1 and R_2 are both methyl.

In some embodiments, the compound is further defined as:



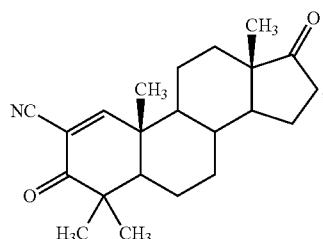
wherein R_{20} , R_{21} , and R_{22} are each independently:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12), amido_(C≤12), alkylimino_(C≤12), alkenylimino_(C≤12), alkynylimino_(C≤12), arylimino_(C≤12), aralkylimino_(C≤12), heteroarylimino_(C≤12), heteroaralkylimino_(C≤12), acylimino_(C≤12), alkylthio_(C≤12), alkenylthio_(C≤12), alkynylthio_(C≤12), arylthio_(C≤12), aralkylthio_(C≤12), heteroarylthio_(C≤12), heteroaralkylthio_(C≤12), acylthio_(C≤12), thioacyl_(C≤12), alkylsulfonyl_(C≤12), alkynylsulfonyl_(C≤12), arylsulfonyl_(C≤12), aralkylsulfonyl_(C≤12), heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12), alkylammonium_(C≤12), alkylsulfonium_(C≤12), alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted version of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, acetals, ketals, prodrugs, or optical isomers thereof.

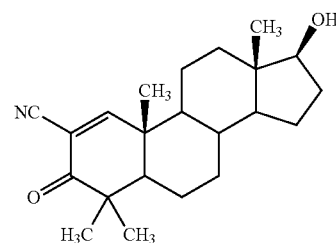
For example, the disclosure provides:



or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

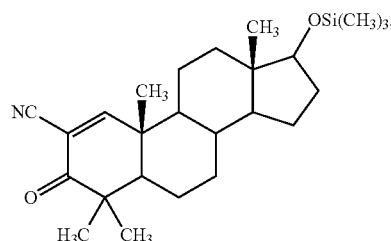
14

For example, the disclosure provides:



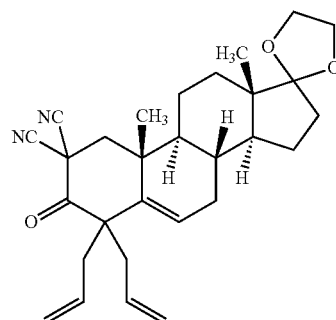
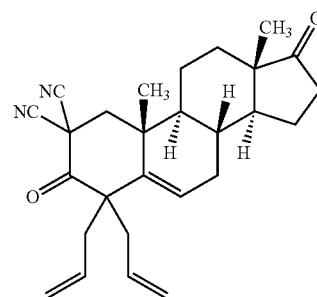
or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

For example, the disclosure provides:



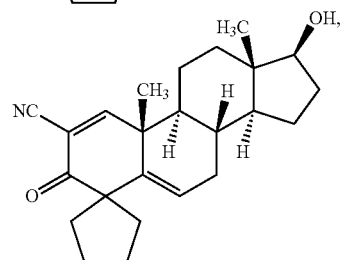
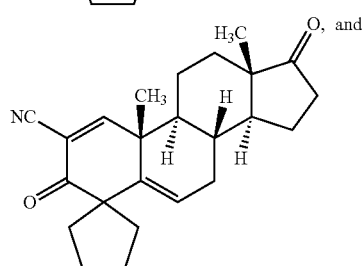
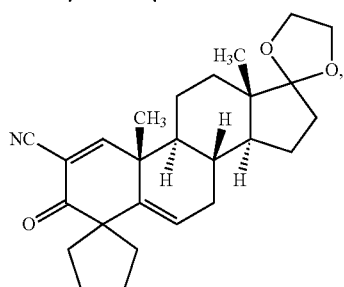
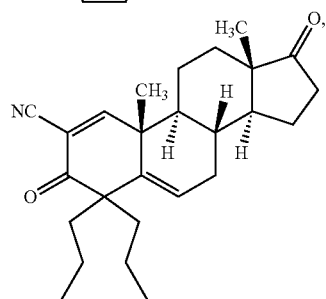
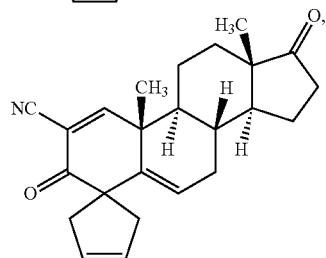
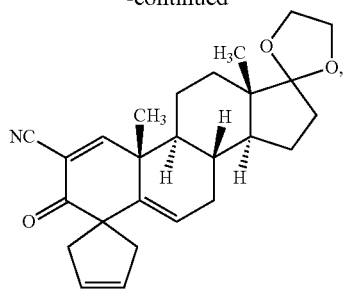
or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

In some embodiments, the disclosure provides compounds selected from the group consisting of:



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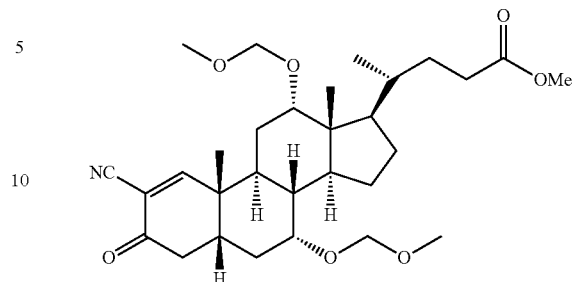
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or pharmaceutically acceptable salts, hydrates, solvates, tau-
tomers, or optical isomers thereof.

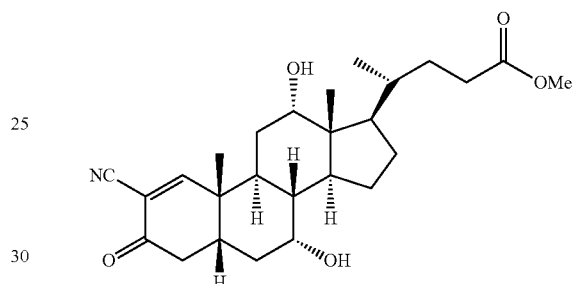
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In some variations, the disclosure provides:



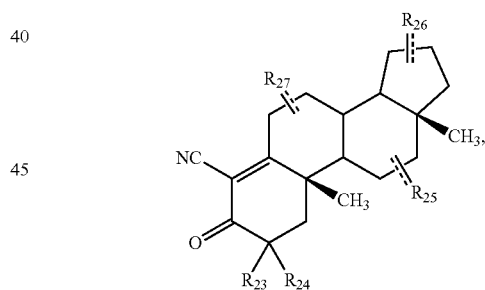
or pharmaceutically acceptable salts, hydrates, solvates, tau-
tomers, or optical isomers thereof.

In some variations, the disclosure provides:



or pharmaceutically acceptable salts, hydrates, solvates, tau-
tomers, or optical isomers thereof.

In another aspect, the disclosure provides compounds of
the formula:



wherein:

R_{23} and R_{24} are each independently:

or hydrogen, alkyl_(C≤8) or substituted alkyl_(C≤8); or

R_{23} and R_{24} are taken together and are alkanediyl_(C≤12),
alkenediyl_(C≤12), alkanediyl_(C≤12) or alkenediyl_(C≤12);

R_{25} , R_{26} and R_{27} are each independently:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino,
nitro, imino, cyano, azido, mercapto, or thio; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),

aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12),

acyl_(C≤12), alkylidene_(C≤12), alkoxy_(C≤12),

alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12),

aralkoxy_(C≤12), heteroaryloxy_(C≤12),

heteroaralkoxy_(C≤12), acyloxy_(C≤12),

alkoxyamino_(C≤12), alkylamino_(C≤12),

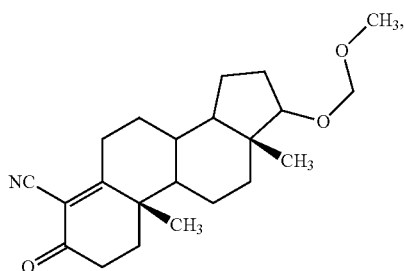
dialkylamino_(C≤12), alkenylamino_(C≤12), alkynylami-

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no_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroaryl amino_(C≤12), heteroaralkylamino_(C≤12), alkylsulfonylamino_(C≤12), amido_(C≤12), alkylimino_(C≤12), alkenylimino_(C≤12), arylimino_(C≤12), aralkylimino_(C≤12), heteroaryl imino_(C≤12), heteroaralkylimino_(C≤12), acylimino_(C≤12), alkylthio_(C≤12), alkenylthio_(C≤12), alkynylthio_(C≤12), arylthio_(C≤12), aralkylthio_(C≤12), heteroarylthio_(C≤12), heteroaralkylthio_(C≤12), acylthio_(C≤12), thioacyl_(C≤12), alkylsulfonyl_(C≤12), alkenylsulfonyl_(C≤12), alkynylsulfonyl_(C≤12), arylsulfonyl_(C≤12), aralkylsulfonyl_(C≤12), heteroarylsulfonyl_(C≤12), heteroaralkylsulfonyl_(C≤12), alkylammonium_(C≤12), alkylsulfonium_(C≤12), alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted version of any of these groups;

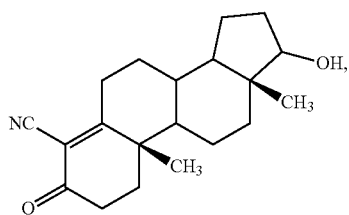
or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, acetals, ketals, prodrugs, or optical isomers thereof.

For example, the disclosure provides:



or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

For example, the disclosure provides:



or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

In some embodiments, the present disclosure provides compounds selected from the group consisting of:

- (S)-3-((1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-4,4-dimethyl-3,5-dioxohepta-1,6-dienyl)-3,5,5-trimethyl-6-oxocyclohex-1-enecarbonitrile,
- (S)-3-((1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-5,5-dimethoxy-4,4-dimethyl-3-oxohepta-1,6-dienyl)-3,5,5-trimethyl-6-oxocyclohex-1-enecarbonitrile,
- (S)-3-((E)-4-(2-(4-hydroxy-3-methoxystyryl)-1,3-dioxolan-2-yl)-4-methyl-3-oxopent-1-enyl)-3,5,5-trimethyl-6-oxocyclohex-1-enecarbonitrile,
- (S)-3-((E)-4-(2-(4-(tert-butyl)dimethylsilyloxy)-3-methoxystyryl)-1,3-dioxolan-2-yl)-4-methyl-3-oxopent-1-enyl)-3,5,5-trimethyl-6-oxocyclohex-1-enecarbonitrile,
- (S,E)-3-(4-hydroxystyryl)-3,5,5-trimethyl-6-oxocyclohex-1-enecarbonitrile,
- (2S,3S)-6-cyano-4-a,8,8-trimethyl-7-oxo-2-(3,4,5-trihydroxyphenyl)-3,4,4a,7,8,8a-hexahydro-2H-chromen-3-yl-3,4,5-trihydroxybenzoate, and

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(2R,3R)-7-cyano-5,5,8a-trimethyl-6-oxo-2-(3,4,5-trihydroxyphenyl)-3,4,4a,5,6,8a-hexahydro-2H-chromen-3-yl-3,4,5-trihydroxybenzoate.

In some embodiments, the present disclosure provides compounds selected from the group consisting of:

(S,E)-3-(4-hydroxystyryl)-3-methyl-6-oxocyclohex-1-enecarbonitrile, and

(3S)-3-(4-hydroxystyryl)-3,5-dimethyl-6-oxocyclohex-1-enecarbonitrile.

In some embodiments, the present disclosure provides compounds selected from the group consisting of:

(10S,13S)-4,4,10,13-tetramethyl-3,17-dioxo-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthrene-2-carbonitrile,

(10S,13S,17S)-17-hydroxy-4,4,10,13-tetramethyl-3-oxo-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthrene-2-carbonitrile, and

(10S,13S)-4,4,10,13-tetramethyl-3-oxo-17-(trimethylsilyloxy)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthrene-2-carbonitrile.

In some embodiments, the present disclosure provides compounds selected from the group consisting of:

(10S,13R)-17-(methoxymethoxy)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-4-carbonitrile, and

(10S,13R)-17-hydroxy-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-4-carbonitrile.

In some embodiments, compounds of the present disclosure are in the form of pharmaceutically acceptable salts. In other embodiments, compounds of the present disclosure are not be in the form of a pharmaceutically acceptable salts.

In some embodiments, compounds of the present disclosure are esters of the above formulas. The ester may, for example, result from a condensation reaction between a hydroxy group of the formula and the carboxylic acid group of biotin.

In some embodiments, the compounds of the present disclosure are present as mixtures of stereoisomers. In other embodiments, the compounds of the present disclosure are present as single stereoisomers.

In some embodiments, compounds of the present disclosure may be used as inhibitors of IFN-γ-induced nitrous oxide (NO) production in macrophages, for example, having an IC₅₀ value of less than 0.2 μM.

Other general aspects of the present disclosure contemplate a pharmaceutical composition comprising as an active ingredient a compound of the present disclosure and a pharmaceutically acceptable carrier. The composition may, for example, be adapted for administration by a route selected from the group consisting of orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intraleisionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intra-pleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularly, intravitreally, lipo-somally, locally, mucosally, orally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof. In particular embodiments, the composition may be formulated for oral delivery. In particular embodiments, the composition is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a wafer, or an elixir. In certain embodi-

ments, the soft capsule is a gelatin capsule. Certain compositions may comprise a protective coating, such as those compositions formulated for oral delivery. Certain compositions further comprise an agent that delays absorption, such as those compositions formulated for oral delivery. Certain compositions may further comprise an agent that enhances solubility or dispersibility, such as those compositions formulated for oral delivery. Certain compositions may comprise a compound of the present disclosure, wherein the compound is dispersed in a liposome, an oil and water emulsion or a water and oil emulsion.

Yet another general aspect of the present disclosure contemplates a therapeutic method comprising administering a pharmaceutically effective compound of the present disclosure to a subject. The subject may, for example, be a human. These or any other methods of the present disclosure may further comprise identifying a subject in need of treatment.

Another method of the present disclosure contemplates a method of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure. The cancer may be any type of cancer, such as a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma. Other types of cancers include cancer of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung, neck, ovary, pancreas, prostate, spleen, small intestine, large intestine, stomach, or testicle. In these or any other methods, the subject may be a primate. This or any other method may further comprise identifying a subject in need of treatment. The subject may have a family or patient history of cancer. In certain embodiments, the subject has symptoms of cancer. The compounds of the invention may be administered via any method described herein, such as locally. In certain embodiments, the compound is administered by direct intratumoral injection or by injection into tumor vasculature. In certain embodiments, the compounds may be administered systemically. The compounds may be administered intravenously, intraarterially, intramuscularly, intraperitoneally, subcutaneously or orally, in certain embodiments.

In certain embodiments regarding methods of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the pharmaceutically effective amount is 0.1-1000 mg/kg. In certain embodiments, the pharmaceutically effective amount is administered in a single dose per day. In certain embodiments, the pharmaceutically effective amount is administered in two or more doses per day. The compound may be administered by contacting a tumor cell during ex vivo purging, for example. The method of treatment may comprise any one or more of the following: a) inducing cytotoxicity in a tumor cell; b) killing a tumor cell; c) inducing apoptosis in a tumor cell; d) inducing differentiation in a tumor cell; or e) inhibiting growth in a tumor cell. The tumor cell may be any type of tumor cell, such as a leukemia cell. Other types of cells include, for example, a bladder cancer cell, a breast cancer cell, a lung cancer cell, a colon cancer cell, a prostate cancer cell, a liver cancer cell, a pancreatic cancer cell, a stomach cancer cell, a testicular cancer cell, a brain cancer cell, an ovarian cancer cell, a lymphatic cancer cell, a skin cancer cell, a brain cancer cell, a bone cancer cell, or a soft tissue cancer cell.

Combination treatment therapy is also contemplated by the present disclosure. For example, regarding methods of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the method may further comprise a

treatment selected from the group consisting of administering a pharmaceutically effective amount of a second drug, radiotherapy, gene therapy, and surgery. Such methods may further comprise (1) contacting a tumor cell with the compound prior to contacting the tumor cell with the second drug, (2) contacting a tumor cell with the second drug prior to contacting the tumor cell with the compound, or (3) contacting a tumor cell with the compound and the second drug at the same time. The second drug may, in certain embodiments, be an antibiotic, anti-inflammatory, anti-neoplastic, anti-proliferative, anti-viral, immunomodulatory, or immunosuppressive. The second drug may be an alkylating agent, androgen receptor modulator, cytoskeletal disruptor, estrogen receptor modulator, histone-deacetylase inhibitor, HMG-CoA reductase inhibitor, prenyl-protein transferase inhibitor, retinoid receptor modulator, topoisomerase inhibitor, or tyrosine kinase inhibitor. In certain embodiments, the second drug is 5-azacitidine, 5-fluorouracil, 9-cis-retinoic acid, actinomycin D, alitretinoin, all-trans-retinoic acid, annamycin, axitinib, belinostat, bevacizumab, bexarotene, bosutinib, busulfan, capecitabine, carboplatin, carmustine, CD437, cediranib, cetuximab, chlorambucil, cisplatin, cyclophosphamide, cytarabine, dacarbazine, dasatinib, daunorubicin, decitabine, docetaxel, dolastatin-10, doxifluridine, doxorubicin, doxorubicin, epirubicin, erlotinib, etoposide, etoposide, gefitinib, gemcitabine, gemtuzumab, ozogamicin, hexamethylmelamine, idarubicin, ifosfamide, imatinib, irinotecan, isotretinoin, ixabepilone, lapatinib, LBH589, lomustine, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, MS-275, neratinib, nilotinib, nitrosourea, oxaliplatin, paclitaxel, plicamycin, procarbazine, semaxanib, semustine, sodium butyrate, sodium phenylacetate, streptozotocin, suberoylanilide hydroxamic acid, sunitinib, tamoxifen, teniposide, thiopeta, tioguanine, topotecan, TRAIL, trastuzumab, tretinoin, trichostatin A, valproic acid, valrubicin, vandetanib, vinblastine, vincristine, vindesine, or vinorelbine.

Methods of treating or preventing a disease with an inflammatory component in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. The disease may be, for example, lupus or rheumatoid arthritis. The disease may be an inflammatory bowel disease, such as Crohn's disease or ulcerative colitis. The disease with an inflammatory component may be a cardiovascular disease. The disease with an inflammatory component may be diabetes, such as type 1 or type 2 diabetes. Compounds of the present disclosure may also be used to treat complications associated with diabetes. Such complications are well-known in the art and include, for example, obesity, hypertension, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, myonecrosis, retinopathy and metabolic syndrome (syndrome X). The disease with an inflammatory component may be a skin disease, such as psoriasis, acne, or atopic dermatitis. Administration of a compound of the present disclosure in treatment methods of such skin diseases may be, for example, topical or oral.

The disease with an inflammatory component may be metabolic syndrome (syndrome X). A patient having this syndrome is characterized as having three or more symptoms selected from the following group of five symptoms: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low high-density lipoprotein cholesterol (HDL); (4) high blood pressure; and (5) elevated fasting glucose, which may be in the range characteristic of Type 2 diabetes if the patient is also diabetic. Each of these symptoms is defined in the Third

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Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670, incorporated herein by reference. Patients with metabolic syndrome, whether or not they have or develop overt diabetes mellitus, have an increased risk of developing the macrovascular and microvascular complications that are listed above that occur with type 2 diabetes, such as atherosclerosis and coronary heart disease.

Another general method of the present disclosure entails a method of treating or preventing a cardiovascular disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure. The cardiovascular disease may be, for example, atherosclerosis, cardiomyopathy, congenital heart disease, congestive heart failure, myocarditis, rheumatic heart disease, valve disease, coronary artery disease, endocarditis, or myocardial infarction. Combination therapy is also contemplated for such methods. For example, such methods may further comprise administering a pharmaceutically effective amount of a second drug. The second drug may be, for example, a cholesterol lowering drug, an anti-hyperlipidemic, a calcium channel blocker, an anti-hypertensive, or an HMG-CoA reductase inhibitor. Non-limiting examples of second drugs include amlodipine, aspirin, ezetimibe, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine or nitrendipine. Other non-limiting examples of second drugs include atenolol, bucindolol, carvedilol, clonidine, doxazosin, indoramin, labetalol, methyldopa, metoprolol, nadolol, oxprenolol, phenoxybenzamine, phentolamine, pindolol, prazosin, propranolol, terazosin, timolol or tolazoline. The second drug may be, for example, a statin, such as atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin.

Methods of treating or preventing a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. The neurodegenerative disease may, for example, be selected from the group consisting of Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), Huntington's disease and amyotrophic lateral sclerosis. In particular embodiments, the neurodegenerative disease is Alzheimer's disease. In particular embodiments, the neurodegenerative disease is MS, such as primary progressive, relapsing-remitting secondary progressive or progressive relapsing MS. The subject may be, for example, a primate. The subject may be a human.

In particular embodiments of methods of treating or preventing a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the treatment suppresses the demyelination of neurons in the subject's brain or spinal cord. In certain embodiments, the treatment suppresses inflammatory demyelination. In certain embodiments, the treatment suppresses the transection of neuron axons in the subject's brain or spinal cord. In certain embodiments, the treatment suppresses the transection of neurites in the subject's brain or spinal cord. In certain embodiments, the treatment suppresses neuronal apoptosis in the subject's brain or spinal cord. In certain embodiments, the treatment stimulates the remyelination of neuron axons in the subject's brain or spinal cord. In certain embodiments, the treatment restores lost function after an MS attack. In certain embodiments, the

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treatment prevents a new MS attack. In certain embodiments, the treatment prevents a disability resulting from an MS attack.

One general aspect of the present disclosure contemplates a method of treating or preventing a disorder characterized by overexpression of iNOS genes in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure.

Another general aspect of the present disclosure contemplates a method of inhibiting IFN- γ -induced nitric oxide production in cells of a subject, comprising administering to said subject a pharmaceutically effective amount of a compound of the present disclosure.

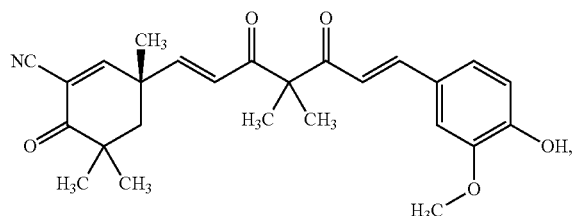
Yet another general method of the present disclosure contemplates a method of treating or preventing a disorder characterized by overexpression of COX-2 genes in a subject, comprising administering to the subject a pharmaceutically effective amount of compound of the present disclosure.

Methods of treating renal/kidney disease (RKD) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. See U.S. patent application Ser. No. 12/352,473, which is incorporated by reference herein in its entirety. The RKD may result from, for example, a toxic insult. The toxic insult may result from, for example, an imaging agent or a drug. The drug may be a chemotherapeutic, for example. The RKD may result from ischemia/reperfusion injury, in certain embodiments. In certain embodiments, the RKD results from diabetes or hypertension. The RKD may result from an autoimmune disease. The RKD may be further defined as chronic RKD, or acute RKD.

In certain methods of treating renal/kidney disease (RKD) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the subject has undergone or is undergoing dialysis. In certain embodiments, the subject has undergone or is a candidate to undergo kidney transplant. The subject may be a primate. The primate may be a human. The subject in this or any other method may be, for example, a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

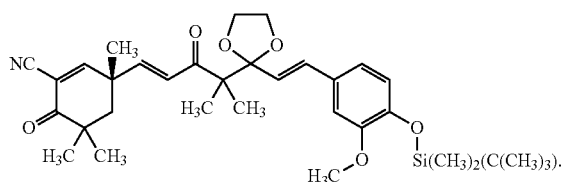
Also contemplated by the present disclosure is a method for improving glomerular filtration rate or creatinine clearance in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure.

Methods of synthesis of compounds of the present disclosure are also contemplated. For example, certain embodiments contemplate a method of making a first compound, wherein the first compound is as follows:



comprising reacting a compound of the following formula with acid:

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Kits are also contemplated by the present disclosure, such as a kit comprising: a compound of the present disclosure; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the compound is to be administered, storage information for the compound, dosing information and instructions regarding how to administer the compound. The kit may comprise a compound of the present disclosure in a multiple dose form.

In certain embodiments, compounds of the present disclosure may be used in preventing and treating diseases and disorders whose pathology involves oxidative stress, inflammation, and dysregulation of inflammatory signaling pathways. In particular embodiments, compounds of the invention may be used in treating diseases and disorders characterized by overexpression of inducible nitric oxide synthase (iNOS), inducible cyclooxygenase (COX-2), or both, in affected tissues; high levels of production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) such as superoxide, hydrogen peroxide, nitric oxide or peroxynitrite; or excessive production of inflammatory cytokines or other inflammation-related proteins such as TNF α , IL-6, IL-1, IL-8, ICAM-1, VCAM-1, and VEGF. Such diseases or disorders may, in some embodiments, involve undesirable proliferation of certain cells, as in the case of cancer (e.g., solid tumors, leukemias, myelomas, lymphomas, and other cancers), fibrosis associated with organ failure, or excessive scarring. Other such disorders include (but are not limited to) autoimmune diseases such as lupus, rheumatoid arthritis, juvenile-onset diabetes, multiple sclerosis, psoriasis, and Crohn's disease; cardiovascular diseases such as atherosclerosis, heart failure, myocardial infarction, acute coronary syndrome, restenosis following vascular surgery, hypertension, and vasculitis; neurodegenerative or neuromuscular diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, and muscular dystrophy; neurological disorders such as epilepsy and dystonia; neuropsychiatric conditions such as major depression, bipolar disorder, post-traumatic stress disorder, schizophrenia, anorexia nervosa, ADHD, and autism-spectrum disorders; retinal diseases such as macular degeneration, diabetic retinopathy, glaucoma, and retinitis; chronic and acute pain syndromes, including inflammatory and neuropathic pain; hearing loss and tinnitus; diabetes and complications of diabetes, including metabolic syndrome, diabetic nephropathy, diabetic neuropathy, and diabetic ulcers; respiratory diseases such as asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, and cystic fibrosis; inflammatory bowel diseases; osteoporosis, osteoarthritis, and other degenerative conditions of bone and cartilage; acute or chronic organ failure, including renal failure, liver failure (including cirrhosis and hepatitis), and pancreatitis; ischemia-reperfusion injury associated with thrombotic or hemorrhagic stroke, subarachnoid hemorrhage, cerebral vasospasm, myocardial infarction, shock, or trauma; complications of organ or tissue transplantation including acute or chronic transplant failure or rejection and graft-versus-host disease; skin diseases

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including atopic dermatitis and acne; sepsis and septic shock; excessive inflammation associated with infection, including respiratory inflammation associated with influenza and upper respiratory infections; mucositis associated with cancer therapy, including radiation therapy or chemotherapy; and severe burns.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula doesn't mean that it cannot also belong to another generic formula.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The invention may be better understood by reference to one of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1-16 and 20-24. Inhibition of NO Production. RAW264.7 macrophages were pre-treated with DMSO or drugs at various concentrations (μ M) for 2 hours, then treated with IFN γ for 24 hours. NO concentration in media was determined using a Griess reagent system; cell viability was determined using the WST-1 reagent.

FIGS. 17-18. Suppression of iNOS mRNA induction. RAW264.7 mouse macrophages were pre-treated for 2 hours with compounds at the indicated concentrations and subsequently stimulated with 10 ng/ml IFN γ for an additional 2 hours. mRNA levels of iNOS were quantified by qPCR and are shown relative to the vehicle-treated IFN γ -stimulated sample which was normalized to a value of 1. Values are averages of duplicate PCR reactions, each with triplicate wells.

FIG. 19. iNOS Western Blot in RAW264.7 mouse macrophages. RAW264.7 cells were pre-treated for 2 hours with indicated compounds and subsequently stimulated with 10 ng/ml IFN γ for an additional 24 hours. iNOS protein levels were assayed by immunoblotting. Actin was used as a loading control.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Disclosed herein are, for example, new compounds with antioxidant and anti-inflammatory properties, methods for their manufacture, and methods for their use, including for the treatment and/or prevention of disease.

I. Definitions

"Basic skeleton" is defined as: (1) the atoms and σ -bonds forming the backbone of each of two rings of an organic compound, e.g., a natural or non-natural product, that are furthest apart from one another when the natural product is drawn as a two-dimensional structural formula, provided that the two rings are connected to one another through at least through one backbone consisting entirely of carbon-carbon

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bonds (e.g., single, double, triple, aromatic, or non-aromatic); and (2) the atoms and σ -bonds of any backbone connecting the two rings defined in (1).

As used herein, “hydrogen” means —H; “hydroxy” means —OH; “oxo” means =O; “halo” means independently —F, —Cl, —Br or —I; “amino” means —NH₂ (see below for definitions of groups containing the term amino, e.g., alkylamino); “hydroxyamino” means —NHOH; “nitro” means —NO₂; imino means =NH (see below for definitions of groups containing the term imino, e.g., alkylamino); “cyano” means —CN; “azido” means —N₃; “mercapto” means —SH; “thio” means —S; “sulfonamido” means —NHS(O)₂— (see below for definitions of groups containing the term sulfonamido, e.g., alkylsulfonamido); “sulfonyl” means —S(O)₂— (see below for definitions of groups containing the term sulfonyl, e.g., alkylsulfonyl); and “silyl” means —SiH₃ (see below for definitions of group(s) containing the term silyl, e.g., alkylsilyl).

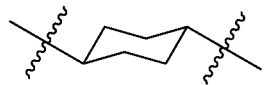
For the groups below, the following parenthetical subscripts further define the groups as follows: “(Cn)” defines the exact number (n) of carbon atoms in the group. “(C≤n)” defines the maximum number (n) of carbon atoms that can be in the group, with the minimum number of carbon atoms in such at least one, but otherwise as small as possible for the group in question. E.g., it is understood that the minimum number of carbon atoms in the group “alkenyl_(C≤8)” is 2. For example, “alkoxy_(C≤10)” designates those alkoxy groups having from 1 to 10 carbon atoms (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (e.g., 3-10 carbon atoms)). (Cn-n') defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Similarly, “alkyl_(C2-10)” designates those alkyl groups having from 2 to 10 carbon atoms (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (e.g., 3-10 carbon atoms)).

The term “alkyl” when used without the “substituted” modifier refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, —CH₃ (Me), —CH₂CH₃ (Et), —CH₂CH₂CH₃ (n-Pr), —CH(CH₃)₂ (iso-Pr), —CH(CH₂)₂ (cyclopropyl), —CH₂CH₂CH₂CH₃ (n-Bu), —CH(CH₃)CH₂CH₃ (sec-butyl), —CH₂CH(CH₃)₂ (iso-butyl), —C(CH₃)₃ (tert-butyl), —CH₂C(CH₃)₃ (neo-pentyl), cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexylmethyl are non-limiting examples of alkyl groups. The term “substituted alkyl” refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkyl groups: —CH₂OH, —CH₂Cl, —CH₂Br, —CH₂SH, —CF₃, —CH₂CN, —CH₂C(O)H, —CH₂C(O)OH, —CH₂C(O)OCH₃, —CH₂C(O)NH₂, —CH₂C(O)NHCH₃, —CH₂C(O)CH₃, —CH₂OCH₃, —CH₂OCH₂CF₃, —CH₂OC(O)CH₃, —CH₂NH₂, —CH₂NHCH₃, —CH₂N(CH₃)₂, —CH₂CH₂Cl, —CH₂CH₂OH, —CH₂CF₃, —CH₂CH₂OC(O)CH₃, —CH₂CH₂NHCO₂C(CH₃)₃, and —CH₂Si(CH₃)₃.

The term “alkanedyl” when used without the “substituted” modifier refers to a non-aromatic divalent group, wherein the alkanedyl group is attached with two σ -bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than

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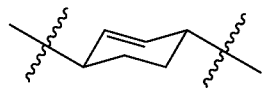
carbon and hydrogen. The groups, —CH₂—(methylene), —CH₂CH₂—, —CH₂C(CH₃)₂CH₂—, —CH₂CH₂CH₂—, and



are non-limiting examples of alkanedyl groups. The term “substituted alkanedyl” refers to a non-aromatic monovalent group, wherein the alkanedyl group is attached with two σ -bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkanedyl groups: —CH(F)—, —CF₂—, —CH(Cl)—, —CH(OH)—, —CH(OCH₃)—, and —CH₂CH(Cl)—.

The term “alkenyl” when used without the “substituted” modifier refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: —CH=CH₂ (vinyl), —CH=CHCH₃, —CH=CHCH₂CH₃, —CH₂CH=CH₂ (allyl), —CH₂CH=CHCH₃, and —CH=CH—C₆H₅. The term “substituted alkenyl” refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, —CH=CHF, —CH=CHCl and —CH=CHBr, are non-limiting examples of substituted alkenyl groups.

The term “alkenedyl” when used without the “substituted” modifier refers to a non-aromatic divalent group, wherein the alkenedyl group is attached with two σ -bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. The groups, —CH=CH—, —CH=C(CH₃)CH₂—, —CH=CHCH₂—, and



are non-limiting examples of alkenedyl groups. The term “substituted alkenedyl” refers to a non-aromatic divalent group, wherein the alkenedyl group is attached with two σ -bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkenedyl groups: —CF=CH—, —C(OH)=CH—, and —CH₂CH=C(Cl)—.

The term “alkynyl” when used without the “substituted” modifier refers to a monovalent group with a nonaromatic

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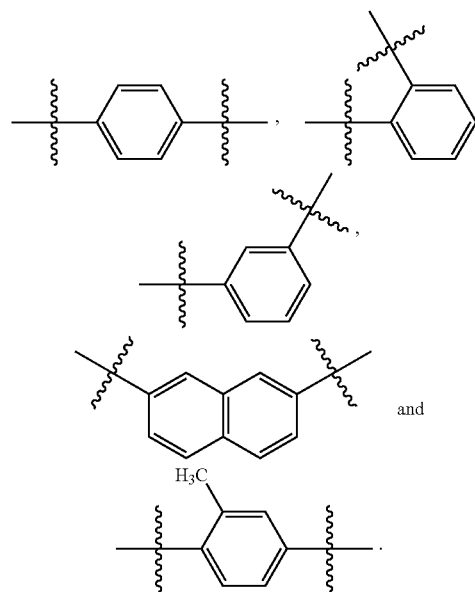
carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. The groups, $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, $-\text{C}\equiv\text{CC}_6\text{H}_5$ and $-\text{CH}_2\text{C}\equiv\text{CCH}_3$, are non-limiting examples of alkynyl groups. The term "substituted alkynyl" refers to a monovalent group with a nonaromatic carbon atom as the point of attachment and at least one carbon-carbon triple bond, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The group, $-\text{C}\equiv\text{CSi}(\text{CH}_3)_3$, is a non-limiting example of a substituted alkynyl group.

The term "alkynediyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkynediyl group is attached with two σ -bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. The groups, $-\text{C}\equiv\text{C}-$, $-\text{C}\equiv\text{CCH}_2-$, and $-\text{C}\equiv\text{CCH}(\text{CH}_3)-$ are non-limiting examples of alkynediyl groups. The term "substituted alkynediyl" refers to a non-aromatic divalent group, wherein the alkynediyl group is attached with two σ -bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups $-\text{C}\equiv\text{CCFH}-$ and $-\text{C}\equiv\text{CHCH}(\text{Cl})-$ are non-limiting examples of substituted alkynediyl groups.

The term "aryl" when used without the "substituted" modifier refers to a monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a six-membered aromatic ring structure wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, $-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_3$ (ethylphenyl), $-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{CH}_3$ (propylphenyl), $-\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$, $-\text{C}_6\text{H}_4\text{CH}(\text{CH}_2)_2$, $-\text{C}_6\text{H}_3(\text{CH}_3)\text{CH}_2\text{CH}_3$ (methylthylphenyl), $-\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$ (vinylphenyl), $-\text{C}_6\text{H}_4\text{CH}=\text{CHCH}_3$, $-\text{C}_6\text{H}_4\text{C}\equiv\text{CH}$, $-\text{C}_6\text{H}_4\text{C}\equiv\text{CCH}_3$, naphthyl, and the monovalent group derived from biphenyl. The term "substituted aryl" refers to a monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a six-membered aromatic ring structure wherein the ring atoms are all carbon, and wherein the monovalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. Non-limiting examples of substituted aryl groups include the groups: $-\text{C}_6\text{H}_4\text{F}$, $-\text{C}_6\text{H}_4\text{Cl}$, $-\text{C}_6\text{H}_4\text{Br}$, $-\text{C}_6\text{H}_4\text{I}$, $-\text{C}_6\text{H}_4\text{OH}$, $-\text{C}_6\text{H}_4\text{OCH}_3$, $-\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_3$, $-\text{C}_6\text{H}_4\text{OC}(\text{O})\text{CH}_3$, $-\text{C}_6\text{H}_4\text{NH}_2$, $-\text{C}_6\text{H}_4\text{NHCH}_3$, $-\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$, $-\text{C}_6\text{H}_4\text{CH}_2\text{OH}$, $-\text{C}_6\text{H}_4\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2$, $-\text{C}_6\text{H}_4\text{CF}_3$, $-\text{C}_6\text{H}_4\text{CN}$, $-\text{C}_6\text{H}_4\text{CHO}$, $-\text{C}_6\text{H}_4\text{CHO}$, $-\text{C}_6\text{H}_4\text{C}(\text{O})\text{CH}_3$, $-\text{C}_6\text{H}_4\text{C}(\text{O})\text{C}_6\text{H}_5$, $-\text{C}_6\text{H}_4\text{CO}_2\text{H}$, $-\text{C}_6\text{H}_4\text{CO}_2\text{CH}_3$, $-\text{C}_6\text{H}_4\text{CONH}_2$, $-\text{C}_6\text{H}_4\text{CONHCH}_3$, and $-\text{C}_6\text{H}_4\text{CON}(\text{CH}_3)_2$.

The term "arenediyl" when used without the "substituted" modifier refers to a divalent group, wherein the arenediyl group is attached with two σ -bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of arenediyl groups include:

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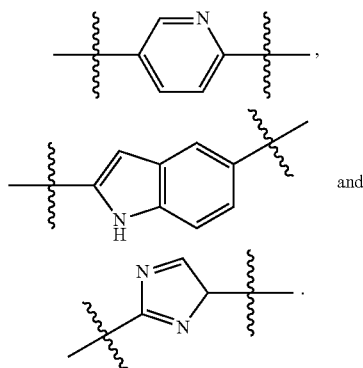
The term "substituted arenediyl" refers to a divalent group, wherein the arenediyl group is attached with two σ -bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic rings structure(s), wherein the ring atoms are all carbon, and wherein the divalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S.

The term "aralkyl" when used without the "substituted" modifier refers to the monovalent group -alkanediyl-aryl, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: phenylmethyl (benzyl, Bn), 1-phenyl-ethyl, 2-phenyl-ethyl, indenyl and 2,3-dihydro-indenyl, provided that indenyl and 2,3-dihydro-indenyl are only examples of aralkyl in so far as the point of attachment in each case is one of the saturated carbon atoms. When the term "aralkyl" is used with the "substituted" modifier, either one or both the alkanediyl and the aryl is substituted. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, 2-oxo-2-phenyl-ethyl (phenylcarbonylmethyl), 2-chloro-2-phenyl-ethyl, chromanyl where the point of attachment is one of the saturated carbon atoms, and tetrahydroquinoliny where the point of attachment is one of the saturated atoms.

The term "heteroaryl" when used without the "substituted" modifier refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the monovalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. Non-limiting examples of aryl groups include acridinyl, furanyl, imidazoimidazolyl, imidazopyrazolyl, imidazopyridinyl, imidazopyrimidinyl, indolyl, indazolyl, methylpyridyl, oxazolyl, phenylimidazolyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, quinolyl, quinazolyl, quinoxalyl, tetrahydroquinolyl, thienyl, triazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyrazinyl, pyrrolotriazinyl, pyrroloimidazolyl, chromenyl (where the point of attachment is one of the aromatic atoms), and chromanyl (where the point of attachment is one

of the aromatic atoms). The term “substituted heteroaryl” refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the monovalent group further has at least one atom independently selected from the group consisting of non-aromatic nitrogen, non-aromatic oxygen, non aromatic sulfur F, Cl, Br, I, Si, and P.

The term “heteroarenediyl” when used without the “substituted” modifier refers to a divalent group, wherein the heteroarenediyl group is attached with two σ -bonds, with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom two aromatic atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of heteroarenediyl groups include:



The term “substituted heteroarenediyl” refers to a divalent group, wherein the heteroarenediyl group is attached with two σ -bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic rings structure(s), wherein the ring atoms are all carbon, and wherein the divalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S.

The term “heteroaralkyl” when used without the “substituted” modifier refers to the monovalent group -alkanediyl-heteroaryl, in which the terms alkanediyl and heteroaryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: pyridylmethyl, and thienylmethyl. When the term “heteroaralkyl” is used with the “substituted” modifier, either one or both the alkanediyl and the heteroaryl is substituted.

The term “acyl” when used without the “substituted” modifier refers to a monovalent group with a carbon atom of a carbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having no additional atoms that are not carbon or hydrogen, beyond the oxygen atom of the carbonyl group. The groups, —CHO, —C(O)CH₃ (acetyl, Ac), —C(O)CH₂CH₃, —C(O)CH₂CH₂CH₃, —C(O)CH(CH₃)₂, —C(O)CH(CH₂)₂, —C(O)C₆H₅, —C(O)C₆H₄CH₃, —C(O)C₆H₄CH₂CH₃, —COC₆H₃(CH₃)₂, and —C(O)CH₂C₆H₅, are non-limiting examples of acyl groups. The term “acyl” therefore encompasses, but is not limited to groups sometimes referred to as “alkyl carbonyl” and “aryl carbonyl” groups. The term “substituted acyl” refers to a monovalent group with a carbon atom

of a carbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having at least one atom, in addition to the oxygen of the carbonyl group, independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, —C(O)CH₂CF₃, —CO₂H (carboxyl), —CO₂CH₃ (methylcarboxyl), —CO₂CH₂CH₃, —CO₂CH₂CH₂CH₃, —CO₂C₆H₅, —CO₂CH(CH₃)₂, —CO₂CH(CH₂)₂, —C(O)NH₂ (carbamoyl), —C(O)NHCH₃, —C(O)NHCH₂CH₃, —CONHCH(CH₃)₂, —CONHCH(CH₂)₂, —CON(CH₃)₂, —CONHCH₂CF₃, —CO-pyridyl, —CO-imidazolyl, and —C(O)N₃, are non-limiting examples of substituted acyl groups. The term “substituted acyl” encompasses, but is not limited to, “heteroaryl carbonyl” groups.

The term “alkylidene” when used without the “substituted” modifier refers to the divalent group —CRR', wherein the alkylidene group is attached with one σ -bond and one π -bond, in which R and R' are independently hydrogen, alkyl, or R and R' are taken together to represent alkanediyl. Non-limiting examples of alkylidene groups include: =CH₂, =CH(CH₂CH₃), and =C(CH₃)₂. The term “substituted alkylidene” refers to the group —CRR', wherein the alkylidene group is attached with one σ -bond and one π -bond, in which R and R' are independently hydrogen, alkyl, substituted alkyl, or R and R' are taken together to represent a substituted alkanediyl, provided that either one of R and R' is a substituted alkyl or R and R' are taken together to represent a substituted alkanediyl.

The term “alkoxy” when used without the “substituted” modifier refers to the group —OR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkoxy groups include: —OCH₃, —OCH₂CH₃, —OCH₂CH₂CH₃, —OCH(CH₃)₂, —OCH(CH₂)₂, —O-cyclopentyl, and —O-cyclohexyl. The term “substituted alkoxy” refers to the group —OR, in which R is a substituted alkyl, as that term is defined above. For example, —OCH₂CF₃ is a substituted alkoxy group.

Similarly, the terms “alkenyloxy”, “alkynyloxy”, “aryloxy”, “aralkoxy”, “heteroaryloxy”, “heteroaralkoxy” and “acyloxy”, when used without the “substituted” modifier, refers to groups, defined as —OR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenyloxy, alkynyloxy, aryloxy, aralkyloxy and acyloxy is modified by “substituted,” it refers to the group —OR, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term “alkylamino” when used without the “substituted” modifier refers to the group —NHR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylamino groups include: —NHCH₃, —NHCH₂CH₃, —NHCH₂CH₂CH₃, —NHCH(CH₃)₂, —NHCH(CH₂)₂, —NHCH₂CH₂CH₂CH₃, —NHCH(CH₃)CH₂CH₃, —NHCH₂CH(CH₃)₂, —NHC(CH₃)₃, —NH-cyclopentyl, and —NH-cyclohexyl. The term “substituted alkylamino” refers to the group —NHR, in which R is a substituted alkyl, as that term is defined above. For example, —NHCH₂CF₃ is a substituted alkylamino group.

The term “dialkylamino” when used without the “substituted” modifier refers to the group —NRR', in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl having two or more saturated carbon atoms, at least two of which are attached to the nitrogen atom. Non-limiting examples of dialkylamino groups include: —NHC(CH₃)₃, —N(CH₃)CH₂CH₃, —N(CH₂CH₃)₂, N-pyrrolidinyl, and N-piperidinyl. The term “substituted dialkylamino” refers to the group —NRR', in

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which R and R' can be the same or different substituted alkyl groups, one of R or R' is an alkyl and the other is a substituted alkyl, or R and R' can be taken together to represent a substituted alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the nitrogen atom.

The terms “alkoxyamino”, “alkenylamino”, “alkynylamino”, “arylamino”, “aralkylamino”, “heteroarylamino”, “heteroaralkylamino”, and “alkylsulfonylamino” when used without the “substituted” modifier, refers to groups, defined as —NHR, in which R is alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and alkylsulfonyl, respectively, as those terms are defined above. A non-limiting example of an arylamino group is —NHC₆H₅. When any of the terms alkoxyamino, alkenylamino, alkynylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino and alkylsulfonylamino is modified by “substituted,” it refers to the group —NHR, in which R is substituted alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and alkylsulfonyl, respectively.

The term “amido” (acylamino), when used without the “substituted” modifier, refers to the group —NHR, in which R is acyl, as that term is defined above. A non-limiting example of an acylamino group is —NHC(O)CH₃. When the term amido is used with the “substituted” modifier, it refers to groups, defined as —NHR, in which R is substituted acyl, as that term is defined above. The groups —NHC(O)OCH₃ and —NHC(O)NHCH₃ are non-limiting examples of substituted amido groups.

The term “alkylimino” when used without the “substituted” modifier refers to the group —NR, wherein the alkylimino group is attached with one σ -bond and one π -bond, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylimino groups include: —NCH₃, —NCH₂CH₃ and —N-cyclohexyl. The term “substituted alkylimino” refers to the group —NR, wherein the alkylimino group is attached with one σ -bond and one π -bond, in which R is a substituted alkyl, as that term is defined above. For example, —NCH₂CF₃ is a substituted alkylimino group.

Similarly, the terms “alkenylimino”, “alkynylimino”, “arylimino”, “aralkylimino”, “heteroarylimino”, “heteroaralkylimino” and “acylimino”, when used without the “substituted” modifier, refers to groups, defined as —NR, wherein the alkylimino group is attached with one σ -bond and one π -bond, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenylimino, alkynylimino, arylimino, aralkylimino and acylimino is modified by “substituted,” it refers to the group —NR, wherein the alkylimino group is attached with one σ -bond and one π -bond, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term “fluoroalkyl” when used without the “substituted” modifier refers to an alkyl, as that term is defined above, in which one or more fluorines have been substituted for hydrogens. The groups, —CH₂F, —CF₃, and —CH₂CF₃ are non-limiting examples of fluoroalkyl groups. The term “substituted fluoroalkyl” refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one fluorine atom, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, Cl, Br, I, Si, P, and S. The following group is a non-limiting example of a substituted fluoroalkyl: —CFHOH.

The term “alkylthio” when used without the “substituted” modifier refers to the group —SR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkyl-

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thio groups include: —SCH₃, —SCH₂CH₃, —SCH₂CH₂CH₃, —SCH(CH₃)₂, —SCH(CH₂)₂, —S-cyclopentyl, and —S-cyclohexyl. The term “substituted alkylthio” refers to the group —SR, in which R is a substituted alkyl, as that term is defined above. For example, —SCH₂CF₃ is a substituted alkylthio group.

Similarly, the terms “alkenylthio”, “alkynylthio”, “arylthio”, “aralkylthio”, “heteroarylthio”, “heteroaralkylthio”, and “acylthio”, when used without the “substituted” modifier, refers to groups, defined as —SR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenylthio, alkynylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, and acylthio is modified by “substituted,” it refers to the group —SR, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term “thioacyl” when used without the “substituted” modifier refers to a monovalent group with a carbon atom of a thiocarbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having no additional atoms that are not carbon or hydrogen, beyond the sulfur atom of the carbonyl group. The groups, —CHS, —C(S)CH₃, —C(S)CH₂CH₃, —C(S)CH₂CH₂CH₃, —C(S)CH(CH₃)₂, —C(S)CH(CH₂)₂, —C(S)C₆H₅, —C(S)C₆H₄CH₃, —C(S)C₆H₄CH₂CH₃, —C(S)C₆H₃(CH₃)₂, and —C(S)CH₂C₆H₅, are non-limiting examples of thioacyl groups. The term “thioacyl” therefore encompasses, but is not limited to, groups sometimes referred to as “alkyl thiocarbonyl” and “aryl thiocarbonyl” groups. The term “substituted thioacyl” refers to a radical with a carbon atom as the point of attachment, the carbon atom being part of a thiocarbonyl group, further having a linear or branched, cyclo, cyclic or acyclic structure, further having at least one atom, in addition to the sulfur atom of the carbonyl group, independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, —C(S)CH₂CF₃, —C(S)O₂H, —C(S)OCH₃, —C(S)OCH₂CH₃, —C(S)OCH₂CH₂CH₃, —C(S)OC₆H₅, —C(S)OCH(CH₃)₂, —C(S)OCH(CH₂)₂, —C(S)NH₂, and —C(S)NHCH₃, are non-limiting examples of substituted thioacyl groups. The term “substituted thioacyl” encompasses, but is not limited to, “heteroaryl thiocarbonyl” groups.

The term “alkylsulfonyl” when used without the “substituted” modifier refers to the group —S(O)₂R, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylsulfonyl groups include: —S(O)₂CH₃, —S(O)₂CH₂CH₃, —S(O)₂CH₂CH₂CH₃, —S(O)₂CH(CH₃)₂, —S(O)₂CH(CH₂)₂, —S(O)₂cyclopentyl, and —S(O)₂cyclohexyl. The term “substituted alkylsulfonyl” refers to the group —S(O)₂R, in which R is a substituted alkyl, as that term is defined above. For example, —S(O)₂CH₂CF₃ is a substituted alkylsulfonyl group.

Similarly, the terms “alkenylsulfonyl”, “alkynylsulfonyl”, “arylsulfonyl”, “aralkylsulfonyl”, “heteroarylsulfonyl”, and “heteroaralkylsulfonyl” when used without the “substituted” modifier, refers to groups, defined as —S(O)₂R, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, respectively, as those terms are defined above. When any of the terms alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl, aralkylsulfonyl, heteroarylsulfonyl, and heteroaralkylsulfonyl is modified by “substituted,” it refers to the group —S(O)₂R, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl and heteroaralkyl, respectively.

The term “alkylammonium” when used without the “substituted” modifier refers to a group, defined as —NH₂R⁺, —NHRR⁺, or —NRR'R''⁺, in which R, R' and R'' are the

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same or different alkyl groups, or any combination of two of R, R' and R" can be taken together to represent an alkanediyl. Non-limiting examples of alkylammonium cation groups include: $\text{—NH}_2(\text{CH}_3)^+$, $\text{—NH}_2(\text{CH}_2\text{CH}_3)^+$, $\text{—NH}_2(\text{CH}_2\text{CH}_2\text{CH}_3)^+$, $\text{—NH}(\text{CH}_3)_2^+$, $\text{—NH}(\text{CH}_2\text{CH}_3)_2^+$, $\text{—NH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2^+$, $\text{—N}(\text{CH}_3)_3^+$, $\text{—N}(\text{CH}_3)(\text{CH}_2\text{CH}_3)_2^+$, $\text{—N}(\text{CH}_3)_2(\text{CH}_2\text{CH}_3)^+$, $\text{—NH}_2\text{C}(\text{CH}_3)^+$, $\text{—NH}(\text{cyclopentyl})_2^+$, and $\text{—NH}_2(\text{cyclohexyl})^+$. The term "substituted alkylammonium" refers $\text{—NH}_2\text{R}^+$, $\text{—NHRR}'^+$, or $\text{—NRR'R}''^+$, in which at least one of R, R' and R" is a substituted alkyl or two of R, R' and R" can be taken together to represent a substituted alkanediyl. When more than one of R, R' and R" is a substituted alkyl, they can be the same or different. Any of R, R' and R" that are not either substituted alkyl or substituted alkanediyl, can be either alkyl, either the same or different, or can be taken together to represent a alkanediyl with two or more carbon atoms, at least two of which are attached to the nitrogen atom shown in the formula.

The term "alkylsulfonium" when used without the "substituted" modifier refers to the group $\text{—SRR}'^+$, in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl. Non-limiting examples of alkylsulfonium groups include: $\text{—SH}(\text{CH}_3)^+$, $\text{—SH}(\text{CH}_2\text{CH}_3)^+$, $\text{—SH}(\text{CH}_2\text{CH}_2\text{CH}_3)^+$, $\text{—S}(\text{CH}_3)_2^+$, $\text{—S}(\text{CH}_2\text{CH}_3)_2^+$, $\text{—S}(\text{CH}_2\text{CH}_2\text{CH}_3)_2^+$, $\text{—SH}(\text{cyclopentyl})^+$, and $\text{—SH}(\text{cyclohexyl})^+$. The term "substituted alkylsulfonium" refers to the group $\text{—SRR}'^+$, in which R and R' can be the same or different substituted alkyl groups, one of R or R' is an alkyl and the other is a substituted alkyl, or R and R' can be taken together to represent a substituted alkanediyl. For example, $\text{—SH}(\text{CH}_2\text{CF}_3)^+$ is a substituted alkylsulfonium group.

The term "alkylsilyl" when used without the "substituted" modifier refers to a monovalent group, defined as $\text{—SiH}_2\text{R}$, $\text{—SiHRR}'$, or $\text{—SiRR'R}''$, in which R, R' and R" can be the same or different alkyl groups, or any combination of two of R, R' and R" can be taken together to represent an alkanediyl. The groups, $\text{—SiH}_2\text{CH}_3$, $\text{—SiH}(\text{CH}_3)_2$, $\text{—Si}(\text{CH}_3)_3$ and $\text{—Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$, are non-limiting examples of unsubstituted alkylsilyl groups. The term "substituted alkylsilyl" refers $\text{—SiH}_2\text{R}$, $\text{—SiHRR}'$, or $\text{—SiRR'R}''$, in which at least one of R, R' and R" is a substituted alkyl or two of R, R' and R" can be taken together to represent a substituted alkanediyl. When more than one of R, R' and R" is a substituted alkyl, they can be the same or different. Any of R, R' and R" that are not either substituted alkyl or substituted alkanediyl, can be either alkyl, either the same or different, or can be taken together to represent a alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the silicon atom.

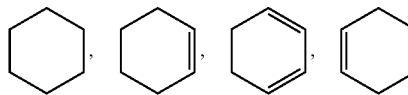
In addition, atoms making up the compounds of the present disclosure are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C . Similarly, it is contemplated that one or more carbon atom(s) of a compound of the present disclosure may be replaced by a silicon atom(s). Furthermore, it is contemplated that one or more oxygen atom(s) of a compound of the present disclosure may be replaced by a sulfur or selenium atom(s).

A compound having a formula that is represented with a dashed bond is intended to include the formulae optionally having zero, one or more double bonds. Thus, for example, the structure

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includes the structures



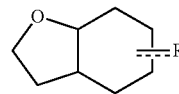
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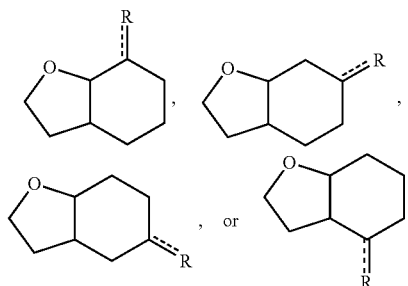
As will be understood by a person of skill in the art, no one such ring atom forms part of more than one double bond.

Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to the atom.

A ring structure shown with an unconnected "R" group, indicates that any implicit hydrogen atom on that ring can be replaced with that R group. In the case of a divalent R group (e.g., oxo, imino, thio, alkylidene, etc.), any pair of implicit hydrogen atoms attached to one atom of that ring can be replaced by that R group. This concept is as exemplified below:



represents



As used herein, a "chiral auxiliary" refers to a removable chiral group that is capable of influencing the stereoselectivity of a reaction. Persons of skill in the art are familiar with such compounds, and many are commercially available.

The use of the word "a" or "an," when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error

for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

The term "effective," as that term is used in the specification and/or claims, means adequate to accomplish a desired, expected, or intended result.

The term "hydrate" when used as a modifier to a compound means that the compound has less than one (e.g., hemihydrate), one (e.g., monohydrate), or more than one (e.g., dihydrate) water molecules associated with each compound molecule, such as in solid forms of the compound.

As used herein, the term "IC₅₀" refers to an inhibitory dose which is 50% of the maximum response obtained.

An "isomer" of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term "patient" or "subject" refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of the present disclosure which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedithionyl sulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, o-(4-hydroxybenzoyl)benzoic acid, oxalic acid, p-chlorobenzenesulfonic acid, phenyl-substituted alkanolic acids, propionic acid, p-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not

critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002).

As used herein, "predominantly one enantiomer" means that a compound contains at least about 85% of one enantiomer, or more preferably at least about 90% of one enantiomer, or even more preferably at least about 95% of one enantiomer, or most preferably at least about 99% of one enantiomer. Similarly, the phrase "substantially free from other optical isomers" means that the composition contains at most about 15% of another enantiomer or diastereomer, more preferably at most about 10% of another enantiomer or diastereomer, even more preferably at most about 5% of another enantiomer or diastereomer, and most preferably at most about 1% of another enantiomer or diastereomer.

"Prevention" or "preventing" includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

"Prodrug" means a compound that is convertible in vivo metabolically into an inhibitor according to the present disclosure. The prodrug itself may or may not also have activity with respect to a given target protein. For example, a compound comprising a hydroxy group may be administered as an ester that is converted by hydrolysis in vivo to the hydroxy compound. Suitable esters that may be converted in vivo into hydroxy compounds include acetates, citrates, lactates, phosphates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis- β -hydroxynaphthoate, gentisates, isethionates, di-p-toluytartrates, methane-sulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexyl-sulfamates, quinate, esters of amino acids, and the like. Similarly, a compound comprising an amine group may be administered as an amide that is converted by hydrolysis in vivo to the amine compound.

The term "saturated" when referring to an atom means that the atom is connected to other atoms only by means of single bonds.

A "stereoisomer" or "optical isomer" is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers.

The invention contemplates that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its R form, S form, or as a mixture of the R and S forms, including racemic and non-racemic mixtures.

"Substituent convertible to hydrogen in vivo" means any group that is convertible to a hydrogen atom by enzymological or chemical means including, but not limited to, hydrolysis and hydrogenolysis. Examples include acyl groups, groups having an oxycarbonyl group, amino acid residues, peptide residues, o-nitrophenylsulfenyl, trimethylsilyl, tetrahydro-pyran, diphenylphosphinyl, hydroxy or alkoxy substituents on imino groups, and the like. Examples of acyl groups include formyl, acetyl, trifluoroacetyl, and the like.

Examples of groups having an oxycarbonyl group include ethoxycarbonyl, tert-butoxycarbonyl ($-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$), benzyloxycarbonyl, p-methoxy-benzyloxycarbonyl, vinyl-oxycarbonyl, β -(p-toluenesulfonyl)ethoxycarbonyl, and the like. Suitable amino acid residues include, but are not limited to, residues of Gly (glycine), Ala (alanine), Arg (arginine), Asn (asparagine), Asp (aspartic acid), Cys (cysteine), Glu (glutamic acid), His (histidine), Ile (isoleucine), Leu (leucine), Lys (lysine), Met (methionine), Phe (phenylalanine), Pro (proline), Ser (serine), Thr (threonine), Trp (tryptophan), Tyr (tyrosine), Val (valine), Nva (norvaline), Hse (homoserine), 4-Hyp (4-hydroxyproline), 5-Hyl (5-hydroxyl-lysine), Orn (ornithine) and β -Ala. Examples of suitable amino acid residues also include amino acid residues that are protected with a protecting group. Examples of suitable protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), tert-butoxycarbonyl groups ($-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$), and the like. Suitable peptide residues include peptide residues comprising two to five, and optionally amino acid residues. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric carbon atom include residues of Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr and Tyr. Peptide residues having an asymmetric carbon atom include peptide residues having one or more constituent amino acid residues having an asymmetric carbon atom. Examples of suitable amino acid protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), tert-butoxycarbonyl groups ($-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$), and the like. Other examples of substituents "convertible to hydrogen in vivo" include reductively eliminable hydrogenolyzable groups. Examples of suitable reductively eliminable hydrogenolyzable groups include, but are not limited to, arylsulfonyl groups (such as o-toluenesulfonyl); methyl groups substituted with phenyl or benzyloxy (such as benzyl, trityl and benzyloxymethyl); arylmethoxycarbonyl groups (such as benzyloxycarbonyl and o-methoxy-benzyloxycarbonyl); and haloethoxycarbonyl groups (such as β , β -trichloroethoxycarbonyl and β -iodoethoxycarbonyl).

"Therapeutically effective amount" or "pharmaceutically effective amount" means that amount which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (e.g., arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (e.g., reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

As used herein, the term "water soluble" means that the compound dissolves in water at least to the extent of 0.010 mole/liter or is classified as soluble according to literature precedence.

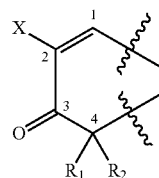
Other abbreviations used herein are as follows: DMSO, dimethyl sulfoxide; NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NGF, nerve

growth factor; IBMX, isobutylmethylxanthine; FBS, fetal bovine serum; GPDH, glycerol 3-phosphate dehydrogenase; RXR, retinoid X receptor; TGF- β , transforming growth factor- β ; IFN γ or IFN- γ , interferon- γ ; LPS, bacterial endotoxin lipopolysaccharide; TNF α or TNF- α , tumor necrosis factor- α ; IL-1 β , interleukin-1 β ; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; TCA, trichloroacetic acid; HO-1, inducible heme oxygenase.

The above definitions supersede any conflicting definition in any of the reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present disclosure.

II. Synthetic Methods

One of the anti-inflammatory pharmacores of the present invention may be represented by the following moiety:

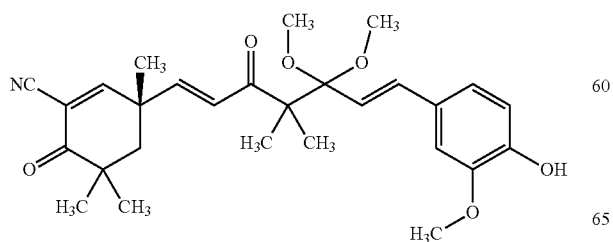
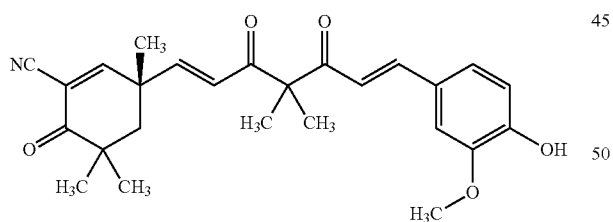


wherein X, R₁ and R₂ are as defined above and in the claim below. This pharmacore is found in a variety of synthetic triterpenoids, such as those described by Honda et al. (2000a); Honda et al., (2000b); Honda et al. (2002); and U.S. application Ser. No. 11/941,820, each of which is incorporated herein by reference. Other compounds comprising such a pharmacore are described in applications filed concurrently with the present application, each of which is incorporated herein by reference: U.S. Patent Application by Eric Anderson, Xin Jiang, Xiaofeng Liu; Melean Visnick, entitled "Antioxidant Inflammation Modulators: Oleanolic Acid Derivatives With Saturation in the C-Ring," filed Apr. 20, 2009; U.S. Patent Application by Eric Anderson, Xin Jiang and Melean Visnick, entitled "Antioxidant Inflammation Modulators: Oleanolic Acid Derivatives with Amino and Other Modifications At C-17," filed Apr. 20, 2009; U.S. Patent Application by Xin Jiang, Jack Greiner, Lester L. Maravetz, Stephen S. Szucs, Melean Visnick, entitled "Antioxidant Inflammation Modulators: Novel Derivatives of Oleanolic Acid," filed Apr. 20, 2009; and U.S. Patent Application by Xin Jiang, Xiaofeng Liu, Jack Greiner, Stephen S. Szucs, Melean Visnick entitled, "Antioxidant Inflammation Modulators: C-17 Homologated Oleanolic Acid Derivatives," filed Apr. 20, 2009. Many of these compounds ("the referenced compounds") have shown a variety of anti-inflammatory-related activities including, for example, anti-proliferative activities and/or antioxidant activities such as induction of heme oxygenase-1 (HO-1) in vitro and in vivo, induction of CD11b expression, inhibition of iNOS induction, inhibition of COX-2 induction, inhibition of NO production, induction of apoptosis in cancer cells, inhibition of NF- κ B, activation of the JNK pathway, and phase 2 induction (elevation of NAD(P)H-quinone oxidoreductase and HO-1). Induction of the Phase 2 response is related to activation of the transcription factor Nrf2, which has been shown to activate the antioxidant response element

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(ARE) in the promoter region of many antioxidant, anti-inflammatory, and cytoprotective genes, and Phase 2 activation is highly correlated with potent inhibition of NO production in activated macrophages (e.g., Dinkova-Kostova et al., *Proc. Natl. Acad. Sci. USA.* 2005; 102(12):4584-9). As (i) compounds of the present invention share a common pharmacore with many of the referenced compounds, and (ii) like the referenced compounds, compounds of the present invention have also been shown to inhibit NO production, compounds of the present invention likely also exhibit one or more of the anti-inflammatory activities displayed by the referenced compounds. As shown herein, introduction of this pharmacore into molecules showing low or modest potency as inhibitors of NO production consistently provides compounds with significantly enhanced potency. For example, compound C0009 has an IC_{50} of 100 nM in the NO assay, vs. the IC_{50} of 1.5 micromolar for the parent compound, curcumin. Similarly, DHEA was inactive in the NO assay (IC_{50} > 10 micromolar), vs. the IC_{50} of 130 nM for compound D0018. Preferably, the modified compound would have an IC_{50} less than 1.25 micromolar. Still more preferably, the modified compound would have an IC_{50} less than 500 nM. In certain embodiments, compounds amenable to the modifications contemplated herein include, but are not limited to, triterpenoids (non-limiting examples include glycyrrhetic acid, boswellic acid, faradiol, calenduladiol, and moronic acid), saponins (e.g., ginsenoside), avicins, resveratrol, curcumin, gossypol, epigallocatechin, epigallocatechin-3-gallate (EGCG), gossypol, lapachol, other flavonoids (non-limiting examples include quercetin, daidzein, luteolin, coumarin, wogonin and baicalin), dehydroandrosterone (DHEA), cholic acid, deoxycholic acid, ginsenoside (e.g., 20(S)-ginsenoside), silymarin, anthocyanins, avenanthramides, cucurbitacins, aloesin, aloë-emodin, and/or tubeimosides.

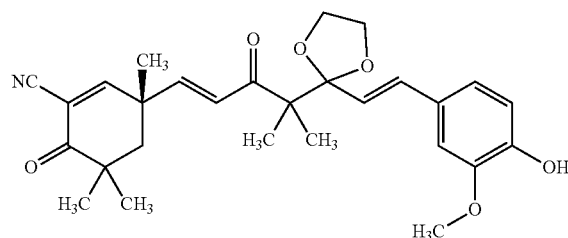
Non-limiting examples of compounds of the present disclosure which contain this particular pharmacore include:



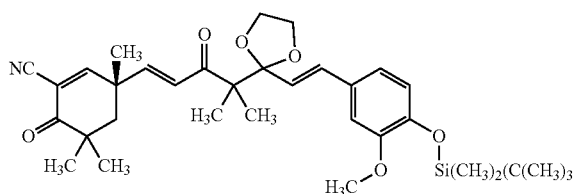
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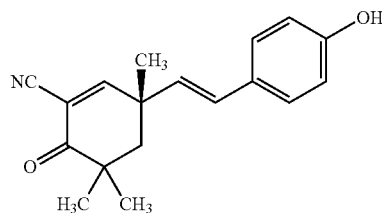
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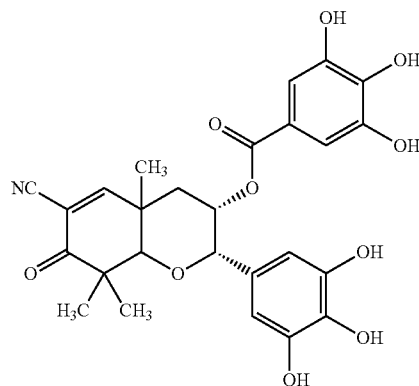
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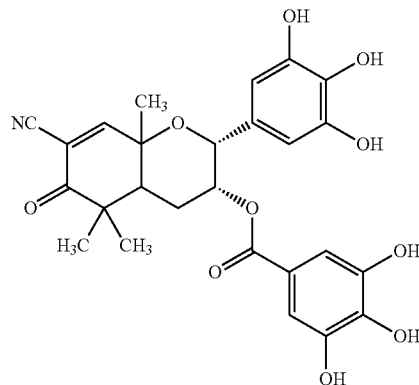
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EGCG 1

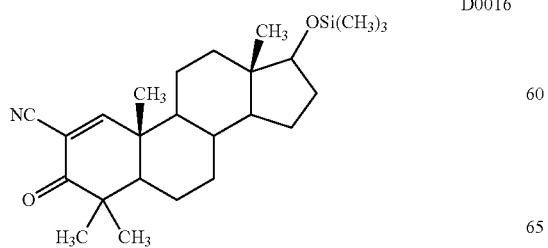
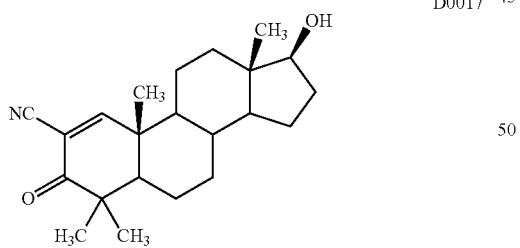
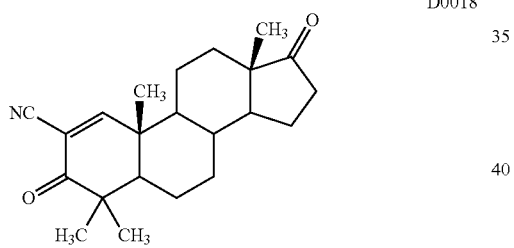
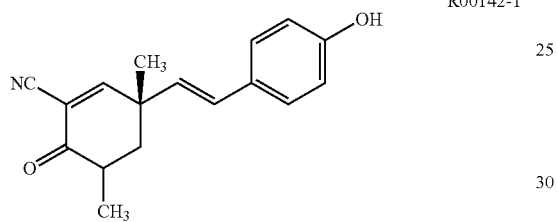
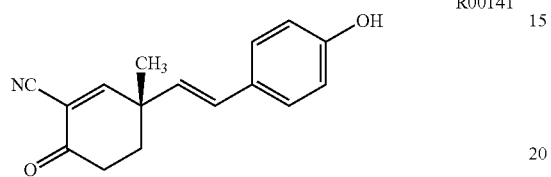
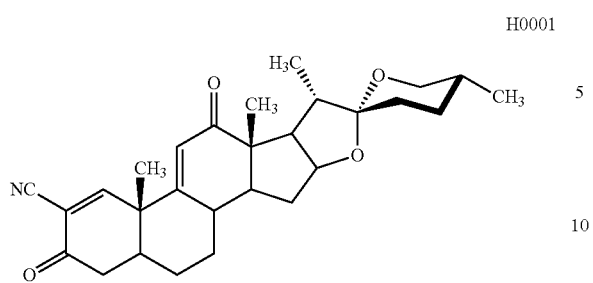


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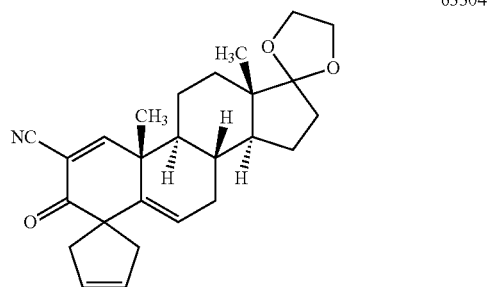
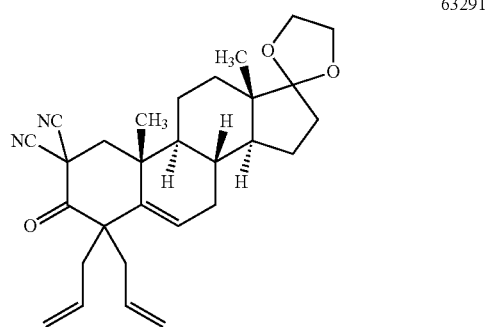
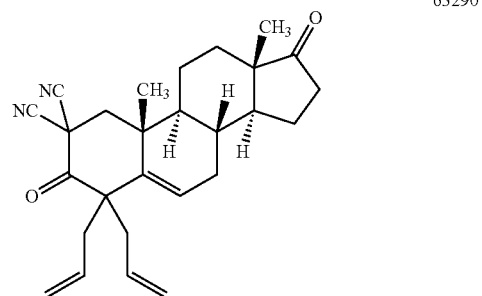
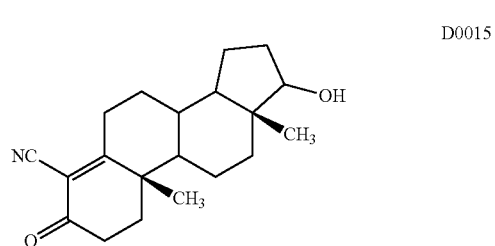
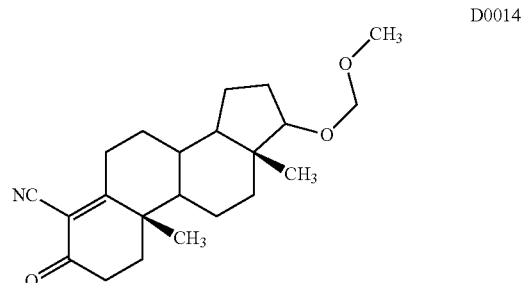


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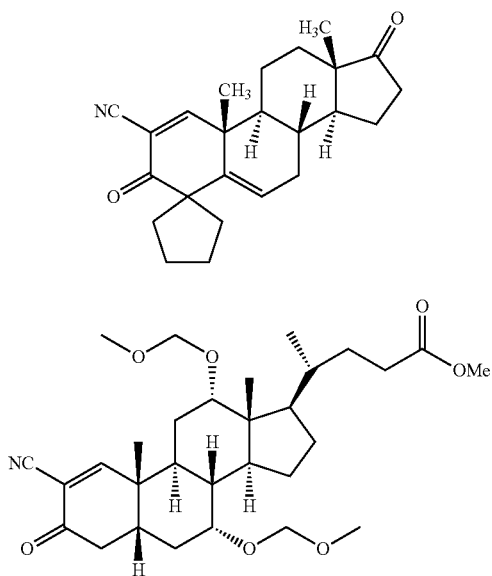
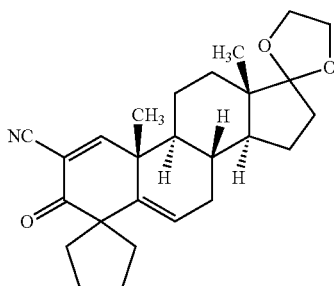
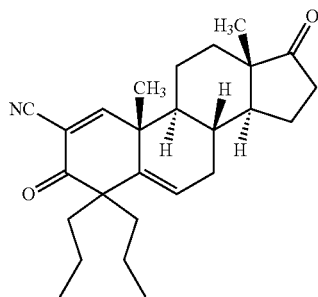
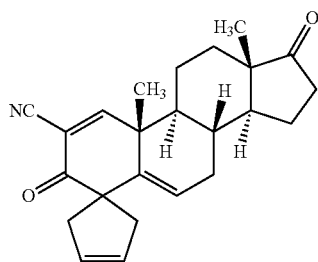
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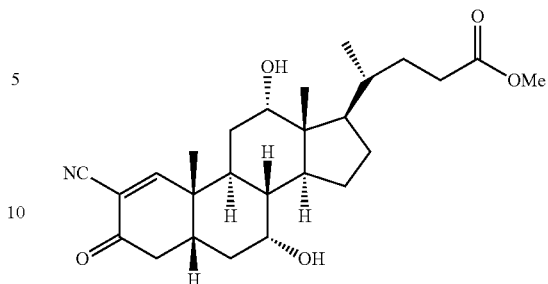
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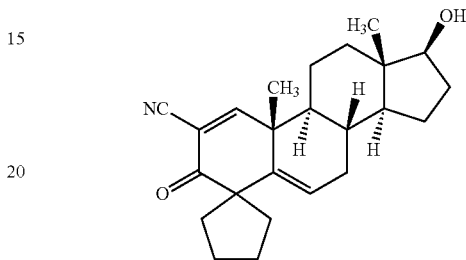
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63311



63314

63313



63329

The compounds of the present disclosure were made using the methods outlined below and in the Examples section (Example 2 and 3). These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (2007), which is incorporated by reference herein.

III. Biological Activity

Compounds of the present disclosure have been tested for inhibition of NO production. The results of these experiments are shown in the figures and in Table 1, below. Experimental details are provided in Example 1.

TABLE 1

Suppression of IFN γ -induced NO production.				
RAW264.7 (20 ng/ml IFN γ)				
Working ID	MW	NO IC ₅₀	WST-1 IC ₅₀	
Curcumin	368.38	1.35 μ M	4 μ M	
C0008	593.83	0.34 μ M	5 μ M	
C0009	435.30	0.1 μ M	1 μ M	
C0010	479.23	0.7 μ M	5 μ M	
Resveratrol	456.70	>10 μ M	>10 μ M	
R00141	253.30	3 μ M	>10 μ M	
R00142	281.35	1.2 μ M	>10 μ M	
R00142-1	267.32	1.6 μ M	>10 μ M	
DHEA	288.42	>10 μ M	>10 μ M	
D0014	357.49	2.4 μ M	>10 μ M	
D0015	313.20	2.9 μ M	>10 μ M	
D0016	413.67	0.15 μ M	10 μ M	
D0017	341.49	0.14 μ M	10 μ M	
D0018	339.47	0.13 μ M	>10 μ M	
Hecogenin	472.66	>10 μ M	>10 μ M	
H0001	449.26	0.15 μ M	2.5 μ M	
63290	416.56	~3 μ M	~10 μ M	
63291	460.61	~1.5 μ M	>10 μ M	
63304	405.53	~30 nM	~400 nM	
63311	361.48	~20 nM	~0.75 μ M	
63313	393.57	~0.45 μ M	~2.5 μ M	
63317	407.55	~70 nM	See FIG. 22	
63318	363.49	~50 nM	See FIG. 23	

TABLE 1-continued

Suppression of IFN γ -induced NO production.			
Working ID	MW	RAW264.7 (20 ng/ml IFN γ)	
		NO IC ₅₀	WST-1 IC ₅₀
63312	531.68	~3.5 μ M	>200 nM
63314	443.59	~8 μ M	>200 nM
63329	365.51	~60 nM	See FIG. 24

IV. Diseases Associated with Inflammation and/or Oxidative Stress

Inflammation is a biological process that provides resistance to infectious or parasitic organisms and the repair of damaged tissue. Inflammation is commonly characterized by localized vasodilation, redness, swelling, and pain, the recruitment of leukocytes to the site of infection or injury, production of inflammatory cytokines such as TNF- α and IL-1, and production of reactive oxygen or nitrogen species such as hydrogen peroxide, superoxide and peroxynitrite. In later stages of inflammation, tissue remodeling, angiogenesis, and scar formation (fibrosis) may occur as part of the wound healing process. Under normal circumstances, the inflammatory response is regulated and temporary and is resolved in an orchestrated fashion once the infection or injury has been dealt with adequately. However, acute inflammation can become excessive and life-threatening if regulatory mechanisms fail. Alternatively, inflammation can become chronic and cause cumulative tissue damage or systemic complications.

Many serious and intractable human diseases involve dysregulation of inflammatory processes, including diseases such as cancer, atherosclerosis, and diabetes, which were not traditionally viewed as inflammatory conditions. In the case of cancer, the inflammatory processes are associated with tumor formation, progression, metastasis, and resistance to therapy. Atherosclerosis, long viewed as a disorder of lipid metabolism, is now understood to be primarily an inflammatory condition, with activated macrophages playing an important role in the formation and eventual rupture of atherosclerotic plaques. Activation of inflammatory signaling pathways has also been shown to play a role in the development of insulin resistance, as well as in the peripheral tissue damage associated with diabetic hyperglycemia. Excessive production of reactive oxygen species and reactive nitrogen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite is a hallmark of inflammatory conditions. Evidence of dysregulated peroxynitrite production has been reported in a wide variety of diseases (Szabo et al., 2007; Schulz et al., 2008; Forstermann, 2006; Pall, 2007).

Autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis, and multiple sclerosis involve inappropriate and chronic activation of inflammatory processes in affected tissues, arising from dysfunction of self vs. non-self recognition and response mechanisms in the immune system. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neural damage is correlated with activation of microglia and elevated levels of pro-inflammatory proteins such as inducible nitric oxide synthase (iNOS). Chronic organ failure such as renal failure, heart failure, and chronic obstructive pulmonary disease is closely associated with the presence of chronic oxidative stress and inflammation, leading to the development of fibrosis and eventual loss of organ function.

Many other disorders involve oxidative stress and inflammation in affected tissues, including inflammatory bowel disease; inflammatory skin diseases; mucositis related to radiation therapy and chemotherapy; eye diseases such as uveitis, glaucoma, macular degeneration, and various forms of retinopathy; transplant failure and rejection; ischemia-reperfusion injury; chronic pain; degenerative conditions of the bones and joints including osteoarthritis and osteoporosis; asthma and cystic fibrosis; seizure disorders; and neuropsychiatric conditions including schizophrenia, depression, bipolar disorder, post-traumatic stress disorder, attention deficit disorders, autism-spectrum disorders, and eating disorders such as anorexia nervosa. Dysregulation of inflammatory signaling pathways is believed to be a major factor in the pathology of muscle wasting diseases including muscular dystrophy and various forms of cachexia.

A variety of life-threatening acute disorders also involve dysregulated inflammatory signaling, including acute organ failure involving the pancreas, kidneys, liver, or lungs, myocardial infarction or acute coronary syndrome, stroke, septic shock, trauma, severe burns, and anaphylaxis.

Many complications of infectious diseases also involve dysregulation of inflammatory responses. Although an inflammatory response can kill invading pathogens, an excessive inflammatory response can also be quite destructive and in some cases can be a primary source of damage in infected tissues. Furthermore, an excessive inflammatory response can also lead to systemic complications due to overproduction of inflammatory cytokines such as TNF- α and IL-1. This is believed to be a factor in mortality arising from severe influenza, severe acute respiratory syndrome, and sepsis.

The aberrant or excessive expression of either iNOS or cyclooxygenase-2 (COX-2) has been implicated in the pathogenesis of many disease processes. For example, it is clear that NO is a potent mutagen (Tamir and Tannebaum, 1996), and that nitric oxide can also activate COX-2 (Salvemini et al., 1994). Furthermore, there is a marked increase in iNOS in rat colon tumors induced by the carcinogen, azoxymethane (Takahashi et al., 1997). A series of synthetic triterpenoid analogs of oleanolic acid have been shown to be powerful inhibitors of cellular inflammatory processes, such as the induction by IFN- γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda et al. (2000a); Honda et al. (2000b), and Honda et al. (2002), which are all incorporated herein by reference.

In one aspect, compounds of the invention are characterized by their ability to inhibit the production of nitric oxide in macrophage-derived RAW 264.7 cells induced by exposure to γ -interferon. They are further characterized by their ability to induce the expression of antioxidant proteins such as NQO1 and reduce the expression of pro-inflammatory proteins such as COX-2 and inducible nitric oxide synthase (iNOS). These properties are relevant to the treatment of a wide array of diseases involving oxidative stress and dysregulation of inflammatory processes including cancer, mucositis resulting from radiation therapy or chemotherapy, autoimmune diseases, cardiovascular diseases including atherosclerosis, ischemia-reperfusion injury, acute and chronic organ failure including renal failure and heart failure, respiratory diseases, diabetes and complications of diabetes, severe allergies, transplant rejection, graft-versus-host disease, neurodegenerative diseases, diseases of the eye and retina, acute and chronic pain, degenerative bone diseases including osteoarthritis and osteoporosis, inflammatory bowel diseases, dermatitis and other skin diseases, sepsis, burns, seizure disorders, and neuropsychiatric disorders.

Without being bound by theory, the activation of the anti-oxidant/anti-inflammatory Keap1/Nrf2/ARE pathway is believed to be implicated in both the anti-inflammatory and anti-carcinogenic properties of the present oleanolic acid derivatives.

In another aspect, compounds of the invention may be used for treating a subject having a condition caused by elevated levels of oxidative stress in one or more tissues. Oxidative stress results from abnormally high or prolonged levels of reactive oxygen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite (formed by the reaction of nitric oxide and superoxide). The oxidative stress may be accompanied by either acute or chronic inflammation. The oxidative stress may be caused by mitochondrial dysfunction, by activation of immune cells such as macrophages and neutrophils, by acute exposure to an external agent such as ionizing radiation or a cytotoxic chemotherapy agent (e.g., doxorubicin), by trauma or other acute tissue injury, by ischemia/reperfusion, by poor circulation or anemia, by localized or systemic hypoxia or hyperoxia, by elevated levels of inflammatory cytokines and other inflammation-related proteins, and/or by other abnormal physiological states such as hyperglycemia or hypoglycemia.

In animal models of many such conditions, stimulating expression of inducible heme oxygenase (HO-1), a target gene of the Nrf2 pathway, has been shown to have a significant therapeutic effect including models of myocardial infarction, renal failure, transplant failure and rejection, stroke, cardiovascular disease, and autoimmune disease (e.g., Sacerdoti et al., 2005; Abraham & Kappas, 2005; Bach, 2006; Araujo et al., 2003; Liu et al., 2006; Ishikawa et al., 2001; Kruger et al., 2006; Satoh et al., 2006; Zhou et al., 2005; Morse and Choi, 2005; Morse and Choi, 2002). This enzyme breaks free heme down into iron, carbon monoxide (CO), and biliverdin (which is subsequently converted to the potent antioxidant molecule, bilirubin).

In another aspect, compounds of this invention may be used in preventing or treating tissue damage or organ failure, acute and chronic, resulting from oxidative stress exacerbated by inflammation. Examples of diseases that fall in this category include: heart failure, liver failure, transplant failure and rejection, renal failure, pancreatitis, fibrotic lung diseases (cystic fibrosis and COPD, among others), diabetes (including complications), atherosclerosis, ischemia-reperfusion injury, glaucoma, stroke, autoimmune disease, autism, macular degeneration, and muscular dystrophy. For example, in the case of autism, studies suggest that increased oxidative stress in the central nervous system may contribute to the development of the disease (Chauhan and Chauhan, 2006).

Evidence also links oxidative stress and inflammation to the development and pathology of many other disorders of the central nervous system, including psychiatric disorders such as psychosis, major depression, and bipolar disorder; seizure disorders such as epilepsy; pain and sensory syndromes such as migraine, neuropathic pain or tinnitus; and behavioral syndromes such as the attention deficit disorders. See, e.g., Dickerson et al., 2007; Hanson et al., 2005; Kendall-Tackett, 2007; Lencz et al., 2007; Dudhgaonkar et al., 2006; Lee et al., 2007; Morris et al., 2002; Ruster et al., 2005; McIver et al., 2005; Sarchielli et al., 2006; Kawakami et al., 2006; Ross et al., 2003, which are all incorporated by reference herein. For example, elevated levels of inflammatory cytokines, including TNF, interferon- γ , and IL-6, are associated with major mental illness (Dickerson et al., 2007). Microglial activation has also been linked to major mental illness. Therefore, downregulating inflammatory cytokines and inhibiting excessive activation of microglia could be beneficial in

patients with schizophrenia, major depression, bipolar disorder, autism-spectrum disorders, and other neuropsychiatric disorders.

Accordingly, in pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation, treatment may comprise administering to a subject a therapeutically effective amount of a compound of this invention, such as those described above or throughout this specification. Treatment may be administered preventively, in advance of a predictable state of oxidative stress (e.g., organ transplantation or the administration of radiation therapy to a cancer patient), or it may be administered therapeutically in settings involving established oxidative stress and inflammation.

The compounds of the invention may be generally applied to the treatment of inflammatory conditions, such as sepsis, dermatitis, autoimmune disease and osteoarthritis. In one aspect, the compounds of this invention may be used to treat inflammatory pain and/or neuropathic pain, for example, by inducing Nrf2 and/or inhibiting NF- κ B.

In one aspect, the compounds of the invention may be used to function as antioxidant inflammation modulators (AIMs) having potent anti-inflammatory properties that mimic the biological activity of cyclopentenone prostaglandins (cyPGs). In one embodiment, the compounds of the invention may be used to control the production of pro-inflammatory cytokines by selectively targeting regulatory cysteine residues (RCRs) on proteins that regulate the transcriptional activity of redox-sensitive transcription factors. Activation of RCRs by cyPGs or AIMs has been shown to initiate a pro-resolution program in which the activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced, and the activities of the pro-oxidant and pro-inflammatory transcription factors NF- κ B and the STATs are suppressed. This increases the production of antioxidant and reductive molecules (e.g., NQO1, HO-1, SOD1, and/or γ -GCS) and/or decreases oxidative stress and the production of pro-oxidant and pro-inflammatory molecules (e.g., iNOS, COX-2, and/or TNF- α).

In some embodiments, the compounds of the invention may be used in the treatment and prevention of diseases such as cancer, inflammation, Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism, amyotrophic lateral sclerosis, autoimmune diseases such as rheumatoid arthritis, lupus, and MS, inflammatory bowel disease, all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide or prostaglandins, and pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation.

Another aspect of inflammation is the production of inflammatory prostaglandins such as prostaglandin E. These molecules promote vasodilation, plasma extravasation, localized pain, elevated temperature, and other symptoms of inflammation. The inducible form of the enzyme COX-2 is associated with their production, and high levels of COX-2 are found in inflamed tissues. Consequently, inhibition of COX-2 may relieve many symptoms of inflammation and a number of important anti-inflammatory drugs (e.g., ibuprofen and celecoxib) act by inhibiting COX-2 activity. Recent research, however, has demonstrated that a class of cyclopentenone prostaglandins (cyPGs) (e.g., 15-deoxy prostaglandin J2, a.k.a. PGJ2) plays a role in stimulating the orchestrated resolution of inflammation (e.g., Rajakari et al., 2007). COX-2 is also associated with the production of cyclopentenone prostaglandins. Consequently, inhibition of COX-2 may interfere with the full resolution of inflammation, potentially promoting the persistence of activated immune cells in tissues and leading to chronic, "smoldering" inflammation. This

effect may be responsible for the increased incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long periods of time.

In one aspect, the compounds of the invention may be used to control the production of pro-inflammatory cytokines within the cell by selectively activating regulatory cysteine residues (RCRs) on proteins that regulate the activity of redox-sensitive transcription factors. Activation of RCRs by cyPGs has been shown to initiate a pro-resolution program in which the activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced and the activities of the pro-oxidant and pro-inflammatory transcription factors NF- κ B and the STATs are suppressed. In some embodiments, this increases the production of antioxidant and reductive molecules (NQO1, HO-1, SOD1, γ -GCS) and decreases oxidative stress and the production of pro-oxidant and pro-inflammatory molecules (iNOS, COX-2, TNF- α). In some embodiments, the compounds of this invention may cause the cells that host the inflammatory event to revert to a non-inflammatory state by promoting the resolution of inflammation and limiting excessive tissue damage to the host.

A. Cancer

Further, the compounds of the present disclosure may be used to induce apoptosis in tumor cells, to induce cell differentiation, to inhibit cancer cell proliferation, to inhibit an inflammatory response, and/or to function in a chemopreventative capacity. For example, the invention provides new compounds that have one or more of the following properties: (1) an ability to induce apoptosis and differentiate both malignant and non-malignant cells, (2) an activity at sub-micromolar or nanomolar levels as an inhibitor of proliferation of many malignant or premalignant cells, (3) an ability to suppress the de novo synthesis of the inflammatory enzyme inducible nitric oxide synthase (iNOS), (4) an ability to inhibit NF- κ B activation, and (5) an ability to induce the expression of heme oxygenase-1 (HO-1).

The levels of iNOS and COX-2 are elevated in certain cancers and have been implicated in carcinogenesis and COX-2 inhibitors have been shown to reduce the incidence of primary colonic adenomas in humans (Rostom et al., 2007; Brown and DuBois, 2005; Crowel et al., 2003). iNOS is expressed in myeloid-derived suppressor cells (MDSCs) (Angulo et al., 2000) and COX-2 activity in cancer cells has been shown to result in the production of prostaglandin E₂ (PGE₂), which has been shown to induce the expression of arginase in MDSCs (Sinha et al., 2007). Arginase and iNOS are enzymes that utilize L-arginine as a substrate and produce L-ornithine and urea, and L-citrulline and NO, respectively. The depletion of arginine from the tumor microenvironment by MDSCs, combined with the production of NO and peroxynitrite has been shown to inhibit proliferation and induce apoptosis of T cells (Bronte et al., 2003). Inhibition of COX-2 and iNOS has been shown to reduce the accumulation of MDSCs, restore cytotoxic activity of tumor-associated T cells, and delay tumor growth (Sinha et al., 2007; Mazzoni et al., 2002; Zhou et al., 2007).

Inhibition of the NF- κ B and JAK/STAT signaling pathways has been implicated as a strategy to inhibit proliferation of cancer epithelial cells and induce their apoptosis. Activation of STAT3 and NF- κ B has been shown to result in suppression of apoptosis in cancer cells, and promotion of proliferation, invasion, and metastasis. Many of the target genes involved in these processes have been shown to be transcriptionally regulated by both NF- κ B and STAT3 (Yu et al., 2007).

In addition to their direct roles in cancer epithelial cells, NF- κ B and STAT3 also have important roles in other cells

found within the tumor microenvironment. Experiments in animal models have demonstrated that NF- κ B is required in both cancer cells and hematopoietic cells to propagate the effects of inflammation on cancer initiation and progression (Greten et al., 2004). NF- κ B inhibition in cancer and myeloid cells reduces the number and size, respectively, of the resultant tumors. Activation of STAT3 in cancer cells results in the production of several cytokines (IL-6, IL-10) which suppress the maturation of tumor-associated dendritic cells (DC). Furthermore, STAT3 is activated by these cytokines in the dendritic cells themselves. Inhibition of STAT3 in mouse models of cancer restores DC maturation, promotes antitumor immunity, and inhibits tumor growth (Kortylewski et al., 2005).

B. Treatment of Multiple Sclerosis

The compounds and methods of this invention may be used for treating patients for multiple sclerosis (MS). MS is known to be an inflammatory condition of the central nervous system (Williams et al., 1994; Merrill and Benvenist, 1996; Genain and Nauser, 1997). Based on several investigations, there is evidence suggesting that inflammatory, oxidative, and/or immune mechanisms are involved in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and MS (Bagasra et al., 1995; McGeer and McGeer, 1995; Simonian and Coyle, 1996; Kaltschmidt et al., 1997). Both reactive astrocytes and activated microglia have been implicated in causation of neurodegenerative disease (NDD) and neuroinflammatory disease (NID); there has been a particular emphasis on microglia as cells that synthesize both NO and prostaglandins as products of the respective enzymes, iNOS and COX-2. De novo formation of these enzymes may be driven by inflammatory cytokines such as interferon- γ or interleukin-1. In turn, excessive production of NO may lead to inflammatory cascades and/or oxidative damage in cells and tissues of many organs, including neurons and oligodendrocytes of the nervous system, with consequent manifestations in AD and MS, and possible PD and ALS (Coyle and Puttfarcken, 1993; Beal, 1996; Merrill and Benvenist, 1996; Simonian and Coyle, 1996; Vodovotz et al., 1996). Epidemiologic data indicate that chronic use of NSAID's which block synthesis of prostaglandins from arachidonate, markedly lower the risk for development of AD (McGeer et al., 1996; Stewart et al., 1997). Thus, agents that block formation of NO and prostaglandins, may be used in approaches to prevention and treatment of NDD. Successful therapeutic candidates for treating such a disease typically require an ability to penetrate the blood-brain barrier. See, for example, U.S. Patent Publication 2009/0060873, which is incorporated by reference herein in its entirety.

C. Neuroinflammation

Neuroinflammation encapsulates the idea that microglial and astrocytic responses and actions in the central nervous system have a fundamentally inflammation-like character, and that these responses are central to the pathogenesis and progression of a wide variety of neurological disorders. This idea originated in the field of Alzheimer's disease (Griffin et al., 1989; Rogers et al., 1988), where it has revolutionized our understanding of this disease (Akiyama et al., 2000). These ideas have been extended to other neurodegenerative diseases (Eikelenboom et al., 2002; Ishizawa and Dickson, 2001), to ischemic/toxic diseases (Gehrmann et al., 1995; Touzani et al., 1999), to tumor biology (Graeber et al., 2002) and even to normal brain development.

Neuroinflammation incorporates a wide spectrum of complex cellular responses that include activation of microglia and astrocytes and induction of cytokines, chemokines, complement proteins, acute phase proteins, oxidative injury, and related molecular processes. These events may have det-

rimental effects on neuronal function, leading to neuronal injury, further glial activation, and ultimately neurodegeneration.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with neuroin-

D. Treatment of Renal Failure

Another aspect of the present disclosure concerns new methods and compounds for the treatment and prevention of renal disease. See U.S. patent application Ser. No. 12/352, 473, which is incorporated by reference herein in its entirety. Renal failure, resulting in inadequate clearance of metabolic waste products from the blood and abnormal concentrations of electrolytes in the blood, is a significant medical problem throughout the world, especially in developed countries. Diabetes and hypertension are among the most important causes of chronic renal failure (CKD), but it is also associated with other conditions such as lupus. Acute renal failure may arise from exposure to certain drugs (e.g., acetaminophen) or toxic chemicals, or from ischemia-reperfusion injury associated with shock or surgical procedures such as transplantation, and may result in chronic renal failure. In many patients, renal failure advances to a stage in which the patient requires regular dialysis or kidney transplantation to continue living. Both of these procedures are highly invasive and associated with significant side effects and quality of life issues. Although there are effective treatments for some complications of renal failure, such as hyperparathyroidism and hyperphosphatemia, no available treatment has been shown to halt or reverse the underlying progression of renal failure. Thus, agents that can improve compromised renal function would represent a significant advance in the treatment of renal failure.

Inflammation contributes significantly to the pathology of CKD. There is also a strong mechanistic link between oxidative stress and renal dysfunction. The NF- κ B signaling pathway plays an important role in the progression of CKD as NF- κ B regulates the transcription of MCP-1, a chemokine that is responsible for the recruitment of monocytes/macrophages resulting in an inflammatory response that ultimately injures the kidney (Wardle, 2001). The Keap1/Nrf2/ARE pathway controls the transcription of several genes encoding antioxidant enzymes, including heme oxygenase-1 (HO-1). Ablation of the Nrf2 gene in female mice results in the development of lupus-like glomerular nephritis (Yoh et al., 2001). Furthermore, several studies have demonstrated that HO-1 expression is induced in response to renal damage and inflammation and that this enzyme and its products—bilirubin and carbon monoxide—play a protective role in the kidney (Nath et al., 2006).

The glomerulus and the surrounding Bowman's capsule constitute the basic functional unit of the kidney. Glomerular filtration rate (GFR) is the standard measure of renal function. Creatinine clearance is commonly used to measure GFR. However, the level of serum creatinine is commonly used as a surrogate measure of creatinine clearance. For instance, excessive levels of serum creatinine are generally accepted to indicate inadequate renal function and reductions in serum creatinine over time are accepted as an indication of improved renal function. Normal levels of creatinine in the blood are approximately 0.6 to 1.2 milligrams (mg) per deciliter (dl) in adult males and 0.5 to 1.1 milligrams per deciliter in adult females.

Acute kidney injury (AKI) can occur following ischemia-reperfusion, treatment with certain pharmacological agents such as cisplatin and rapamycin, and intravenous injection of

radiocontrast media used in medical imaging. As in CKD, inflammation and oxidative stress contribute to the pathology of AKI. The molecular mechanisms underlying radiocontrast-induced nephropathy (RCN) are not well understood; however, it is likely that a combination of events including prolonged vasoconstriction, impaired kidney autoregulation, and direct toxicity of the contrast media all contribute to renal failure (Tumlin et al., 2006). Vasoconstriction results in decreased renal blood flow and causes ischemia-reperfusion and the production of reactive oxygen species. HO-1 is strongly induced under these conditions and has been demonstrated to prevent ischemia-reperfusion injury in several different organs, including the kidney (Nath et al., 2006). Specifically, induction of HO-1 has been shown to be protective in a rat model of RCN (Goodman et al., 2007). Reperfusion also induces an inflammatory response, in part through activation of NF- κ B signaling (Nichols, 2004). Targeting NF- κ B has been proposed as a therapeutic strategy to prevent organ damage (Zingarelli et al., 2003).

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with renal failure.

E. Cardiovascular Disease

The compounds and methods of this invention may be used for treating patients with cardiovascular disease. See U.S. patent application Ser. No. 12/352,473, which is incorporated by reference herein in its entirety. Cardiovascular (CV) disease is among the most important causes of mortality worldwide, and is the leading cause of death in many developed nations. The etiology of CV disease is complex, but the majority of causes are related to inadequate or completely disrupted supply of blood to a critical organ or tissue. Frequently such a condition arises from the rupture of one or more atherosclerotic plaques, which leads to the formation of a thrombus that blocks blood flow in a critical vessel. Such thrombosis is the principal cause of heart attacks, in which one or more of the coronary arteries is blocked and blood flow to the heart itself is disrupted. The resulting ischemia is highly damaging to cardiac tissue, both from lack of oxygen during the ischemic event and from excessive formation of free radicals after blood flow is restored (a phenomenon known as ischemia-reperfusion injury). Similar damage occurs in the brain during a thrombotic stroke, when a cerebral artery or other major vessel is blocked by thrombosis. Hemorrhagic strokes, in contrast, involve rupture of a blood vessel and bleeding into the surrounding brain tissue. This creates oxidative stress in the immediate area of the hemorrhage, due to the presence of large amounts of free heme and other reactive species, and ischemia in other parts of the brain due to compromised blood flow. Subarachnoid hemorrhage, which is frequently accompanied by cerebral vasospasm, also causes ischemia/reperfusion injury in the brain.

Alternatively, atherosclerosis may be so extensive in critical blood vessels that stenosis (narrowing of the arteries) develops and blood flow to critical organs (including the heart) is chronically insufficient. Such chronic ischemia can lead to end-organ damage of many kinds, including the cardiac hypertrophy associated with congestive heart failure.

Atherosclerosis, the underlying defect leading to many forms of cardiovascular disease, occurs when a physical defect or injury to the lining (endothelium) of an artery triggers an inflammatory response involving the proliferation of vascular smooth muscle cells and the infiltration of leukocytes into the affected area. Ultimately, a complicated lesion known as an atherosclerotic plaque may form, composed of

the above-mentioned cells combined with deposits of cholesterol-bearing lipoproteins and other materials (e.g., Hansson et al., 2006).

Pharmaceutical treatments for cardiovascular disease include preventive treatments, such as the use of drugs intended to lower blood pressure or circulating levels of cholesterol and lipoproteins, as well as treatments designed to reduce the adherent tendencies of platelets and other blood cells (thereby reducing the rate of plaque progression and the risk of thrombus formation). More recently, drugs such as streptokinase and tissue plasminogen activator have been introduced and are used to dissolve the thrombus and restore blood flow. Surgical treatments include coronary artery bypass grafting to create an alternative blood supply, balloon angioplasty to compress plaque tissue and increase the diameter of the arterial lumen, and carotid endarterectomy to remove plaque tissue in the carotid artery. Such treatments, especially balloon angioplasty, may be accompanied by the use of stents, expandable mesh tubes designed to support the artery walls in the affected area and keep the vessel open. Recently, the use of drug-eluting stents has become common in order to prevent post-surgical restenosis (narrowing of the artery) in the affected area. These devices are wire stents coated with a biocompatible polymer matrix containing a drug that inhibits cell proliferation (e.g., paclitaxel or rapamycin). The polymer allows a slow, localized release of the drug in the affected area with minimal exposure of non-target tissues. Despite the significant benefits offered by such treatments, mortality from cardiovascular disease remains high and significant unmet needs in the treatment of cardiovascular disease remain.

As noted above, induction of HO-1 has been shown to be beneficial in a variety of models of cardiovascular disease, and low levels of HO-1 expression have been clinically correlated with elevated risk of CV disease. Compounds of the invention, therefore, may be used in treating or preventing a variety of cardiovascular disorders including but not limited to atherosclerosis, hypertension, myocardial infarction, chronic heart failure, stroke, subarachnoid hemorrhage, and restenosis.

F. Diabetes

Diabetes is a complex disease characterized by the body's failure to regulate circulating levels of glucose. See U.S. patent application Ser. No. 12/352,473, which is incorporated by reference herein in its entirety. This failure may result from a lack of insulin, a peptide hormone that regulates the both the production and absorption of glucose in various tissues. Deficient insulin compromises the ability of muscle, fat, and other tissues to absorb glucose properly, leading to hyperglycemia (abnormally high levels of glucose in the blood). Most commonly, such insulin deficiency results from inadequate production in the islet cells of the pancreas. In the majority of cases this arises from autoimmune destruction of these cells, a condition known as type 1 or juvenile-onset diabetes, but may also be due to physical trauma or some other cause.

Diabetes may also arise when muscle and fat cells become less responsive to insulin and do not absorb glucose properly, resulting in hyperglycemia. This phenomenon is known as insulin resistance, and the resulting condition is known as Type 2 diabetes. Type 2 diabetes, the most common type, is highly associated with obesity and hypertension. Obesity is associated with an inflammatory state of adipose tissue that is thought to play a major role in the development of insulin resistance (e.g., Hotamisligil, 2006; Guilherme et al., 2008).

Diabetes is associated with damage to many tissues, largely because hyperglycemia (and hypoglycemia, which can result from excessive or poorly timed doses of insulin) is

a significant source of oxidative stress. Chronic kidney failure, retinopathy, peripheral neuropathy, peripheral vasculitis, and the development of dermal ulcers that heal slowly or not at all are among the common complications of diabetes. Because of their ability to protect against oxidative stress, particularly by the induction of HO-1 expression, compounds of the invention may be used in treatments for many complications of diabetes. As noted above (Cai et al., 2005), chronic inflammation and oxidative stress in the liver are suspected to be primary contributing factors in the development of Type 2 diabetes. Furthermore, PPAR γ agonists such as thiazolidinediones are capable of reducing insulin resistance and are known to be effective treatments for Type 2 diabetes.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with neuroinflammation.

The effect of treatment of diabetes may be evaluated as follows. Both the biological efficacy of the treatment modality as well as the clinical efficacy are evaluated, if possible. For example, disease manifests itself by increased blood sugar, the biological efficacy of the treatment therefore can be evaluated, for example, by observation of return of the evaluated blood glucose towards normal. Measuring a clinical endpoint which can give an indication of β -cell regeneration after, for example, a six-month period of time, can give an indication of the clinical efficacy of the treatment regimen.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with diabetes.

G. Rheumatoid Arthritis

The compounds and methods of this invention may be used for treating patients with RA. Typically the first signs of rheumatoid arthritis (RA) appear in the synovial lining layer, with proliferation of synovial fibroblasts and their attachment to the articular surface at the joint margin (Lipsky, 1998). Subsequently, macrophages, T cells and other inflammatory cells are recruited into the joint, where they produce a number of mediators, including the cytokines interleukin-1 (IL-1), which contributes to the chronic sequelae leading to bone and cartilage destruction, and tumour necrosis factor (TNF- α), which plays a role in inflammation (Dinarello, 1998; Arend and Dayer, 1995; van den Berg, 2001). The concentration of IL-1 in plasma is significantly higher in patients with RA than in healthy individuals and, notably, plasma IL-1 levels correlate with RA disease activity (Eastgate et al., 1988). Moreover, synovial fluid levels of IL-1 are correlated with various radiographic and histologic features of RA (Kahle et al., 1992; Rooney et al., 1990).

In normal joints, the effects of these and other proinflammatory cytokines are balanced by a variety of anti-inflammatory cytokines and regulatory factors (Burger and Dayer, 1995). The significance of this cytokine balance is illustrated in juvenile RA patients, who have cyclical increases in fever throughout the day (Prieur et al., 1987). After each peak in fever, a factor that blocks the effects of IL-1 is found in serum and urine. This factor has been isolated, cloned and identified as IL-1 receptor antagonist (IL-1ra), a member of the IL-1 gene family (Hannum et al., 1990). IL-1ra, as its name indicates, is a natural receptor antagonist that competes with IL-1 for binding to type I IL-1 receptors and, as a result, blocks the effects of IL-1 (Arend et al., 1998). A 10- to 100-fold excess of IL-1ra may be needed to block IL-1 effectively; however, synovial cells isolated from patients with RA do not appear to produce enough IL-1ra to counteract the effects of IL-1 (Firestein et al., 1994; Fujikawa et al., 1995).

H. Psoriatic Arthritis

Psoriasis is an inflammatory and proliferative skin disorder with a prevalence of 1.5-3%. Approximately 20% of patients with psoriasis develop a characteristic form of arthritis that has several patterns (Gladman, 1992; Jones et al., 1994; Gladman et al., 1995). Some individuals present with joint symptoms first but in the majority, skin psoriasis presents first. About one-third of patients have simultaneous exacerbations of their skin and joint disease (Gladman et al., 1987) and there is a topographic relationship between nail and distal interphalangeal joint disease (Jones et al., 1994; Wright, 1956). Although the inflammatory processes which link skin, nail and joint disease remain elusive, an immune-mediated pathology is implicated.

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy characterized by the association of arthritis and psoriasis and was recognized as a clinical entity distinct from rheumatoid arthritis (RA) in 1964 (Blumberg et al., 1964). Subsequent studies have revealed that PsA shares a number of genetic, pathogenic and clinical features with other spondyloarthropathies (SpAs), a group of diseases that comprise ankylosing spondylitis, reactive arthritis and enteropathic arthritis (Wright, 1979). The notion that PsA belongs to the SpA group has recently gained further support from imaging studies demonstrating widespread enthesitis in the, including PsA but not RA (McGonagle et al., 1999; McGonagle et al., 1998). More specifically, enthesitis has been postulated to be one of the earliest events occurring in the SpAs, leading to bone remodeling and ankylosis in the spine, as well as to articular synovitis when the inflamed entheses are close to peripheral joints. However, the link between enthesitis and the clinical manifestations in PsA remains largely unclear, as PsA can present with fairly heterogeneous patterns of joint involvement with variable degrees of severity (Marsal et al., 1999; Salvarani et al., 1998). Thus, other factors must be posited to account for the multifarious features of PsA, only a few of which (such as the expression of the HLA-B27 molecule, which is strongly associated with axial disease) have been identified. As a consequence, it remains difficult to map the disease manifestations to specific pathogenic mechanisms, which means that the treatment of this condition remains largely empirical.

Family studies have suggested a genetic contribution to the development of PsA (Moll and Wright, 1973). Other chronic inflammatory forms of arthritis, such as ankylosing spondylitis and rheumatoid arthritis, are thought to have a complex genetic basis. However, the genetic component of PsA has been difficult to assess for several reasons. There is strong evidence for a genetic predisposition to psoriasis alone that may mask the genetic factors that are important for the development of PsA. Although most would accept PsA as a distinct disease entity, at times there is a phenotypic overlap with rheumatoid arthritis and ankylosing spondylitis. Also, PsA itself is not a homogeneous condition and various subgroups have been proposed.

Increased amounts of TNF- α have been reported in both psoriatic skin (Ettehadi et al., 1994) and synovial fluid (Partsch et al., 1997). Recent trials have shown a positive benefit of anti-TNF treatment in both PsA (Mease et al., 2000) and ankylosing spondylitis (Brandt et al., 2000).

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with psoriatic arthritis.

I. Reactive Arthritis

In reactive arthritis (ReA) the mechanism of joint damage is unclear, but it is likely that cytokines play critical roles. A

more prevalent Th1 profile high levels of interferon gamma (IFN- γ) and low levels of interleukin 4 (IL-4) has been reported (Lahesmaa et al., 1992; Schlaak et al., 1992; Simon et al., 1993; Schlaak et al., 1996; Kotake et al., 1999; Ribbens et al., 2000), but several studies have shown relative predominance of IL-4 and IL-10 and relative lack of IFN- γ and tumour necrosis factor alpha (TNF- α) in the synovial membrane (Simon et al., 1994; Yin et al., 1999) and fluid (SF) (Yin et al., 1999; Yin et al., 1997) of reactive arthritis patients compared with rheumatoid arthritis (RA) patients. A lower level of TNF- α secretion in reactive arthritis than in RA patients has also been reported after ex vivo stimulation of peripheral blood mononuclear cells (PBMC) (Braun et al., 1999).

It has been argued that clearance of reactive arthritis-associated bacteria requires the production of appropriate levels of IFN- γ and TNF- α , while IL-10 acts by suppressing these responses (Autenrieth et al., 1994; Sieper and Braun, 1995). IL-10 is a regulatory cytokine that inhibits the synthesis of IL-12 and TNF- γ by activated macrophages (de Waal et al., 1991; Hart et al., 1995; Chomarat et al., 1995) and of IFN- γ by T cells (Macatonia et al., 1993).

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with reactive arthritis.

J. Enteropathic Arthritis

Typically enteropathic arthritis (EA) occurs in combination with inflammatory bowel diseases (IBD) such as Crohn's disease or ulcerative colitis. It also can affect the spine and sacroiliac joints. Enteropathic arthritis involves the peripheral joints, usually in the lower extremities such as the knees or ankles. It commonly involves only a few or a limited number of joints and may closely follow the bowel condition. This occurs in approximately 11% of patients with ulcerative colitis and 21% of those with Crohn's disease. The synovitis is generally self-limited and non-deforming.

Enteropathic arthropathies comprise a collection of rheumatologic conditions that share a link to GI pathology. These conditions include reactive (i.e., infection-related) arthritis due to bacteria (e.g., *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia* species, *Clostridium difficile*), parasites (e.g., *Strongyloides stercoralis*, *Taenia saginata*, *Giardia lamblia*, *Ascaris lumbricoides*, *Cryptosporidium* species), and spondyloarthropathies associated with inflammatory bowel disease (IBD). Other conditions and disorders include intestinal bypass (jejunoileal), arthritis, celiac disease, Whipple disease, and collagenous colitis.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with enteropathic arthritis.

K. Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis (JRA), a term for the most prevalent form of arthritis in children, is applied to a family of illnesses characterized by chronic inflammation and hypertrophy of the synovial membranes. The term overlaps, but is not completely synonymous, with the family of illnesses referred to as juvenile chronic arthritis and/or juvenile idiopathic arthritis in Europe.

Both innate and adaptive immune systems use multiple cell types, a vast array of cell surface and secreted proteins, and interconnected networks of positive and negative feedback (Lo et al., 1999). Furthermore, while separable in thought, the innate and adaptive wings of the immune system are functionally intersected (Fearon and Locksley, 1996), and pathologic events occurring at these intersecting points are likely to

be highly relevant to our understanding of pathogenesis of adult and childhood forms of chronic arthritis (Warrington, et al., 2001).

Polyarticular JRA is a distinct clinical subtype characterized by inflammation and synovial proliferation in multiple joints (four or more), including the small joints of the hands (Jarvis, 2002). This subtype of JRA may be severe, because of both its multiple joint involvement and its capacity to progress rapidly over time. Although clinically distinct, polyarticular JRA is not homogeneous, and patients vary in disease manifestations, age of onset, prognosis, and therapeutic response. These differences very likely reflect a spectrum of variation in the nature of the immune and inflammatory attack that can occur in this disease (Jarvis, 1998).

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with JRA.

L. Early Inflammatory Arthritis

The compounds and methods of this invention may be used for treating patients with early inflammatory arthritis. The clinical presentation of different inflammatory arthropathies is similar early in the course of disease. As a result, it is often difficult to distinguish patients who are at risk of developing the severe and persistent synovitis that leads to erosive joint damage from those whose arthritis is more self-limited. Such distinction is critical in order to target therapy appropriately, treating aggressively those with erosive disease and avoiding unnecessary toxicity in patients with more self-limited disease. Current clinical criteria for diagnosing erosive arthropathies such as rheumatoid arthritis (RA) are less effective in early disease and traditional markers of disease activity such as joint counts and acute phase response do not adequately identify patients likely to have poor outcomes (Harrison et al., 1998). Parameters reflective of the pathologic events occurring in the synovium are most likely to be of significant prognostic value.

Recent efforts to identify predictors of poor outcome in early inflammatory arthritis have identified the presence of RA specific autoantibodies, in particular antibodies towards citrullinated peptides, to be associated with erosive and persistent disease in early inflammatory arthritis cohorts. On the basis of this, a cyclical citrullinated peptide (CCP) has been developed to assist in the identification of anti-CCP antibodies in patient sera. Using this approach, the presence of anti-CCP antibodies has been shown to be specific and sensitive for RA, can distinguish RA from other arthropathies, and can potentially predict persistent, erosive synovitis before these outcomes become clinically manifest. Importantly, anti-CCP antibodies are often detectable in sera many years prior to clinical symptoms suggesting that they may be reflective of subclinical immune events (Nielen et al., 2004; Rantapää-Dahlqvist et al., 2003).

M. Ankylosing Spondylitis

AS is a disease subset within a broader disease classification of spondyloarthropathy. Patients affected with the various subsets of spondyloarthropathy have disease etiologies that are often very different, ranging from bacterial infections to inheritance. Yet, in all subgroups, the end result of the disease process is axial arthritis. Despite the early clinically differences seen in the various patient populations, many of them end up nearly identical after a disease course of ten-to-twenty years. Recent studies suggest the mean time to clinical diagnosis of ankylosing spondylitis from disease onset of disease is 7.5 years (Khan, 1998). These same studies suggest that the spondyloarthropathies may have prevalence close to that of rheumatoid arthritis (Feldtkeller et al., 2003; Doran et al., 2003).

AS is a chronic systemic inflammatory rheumatic disorder of the axial skeleton with or without extraskeletal manifestations. Sacroiliac joints and the spine are primarily affected, but hip and shoulder joints, and less commonly peripheral joints or certain extra-articular structures such as the eye, vasculature, nervous system, and gastrointestinal system may also be involved. Its etiology is not yet fully understood (Wordsworth, 1995; Calin and Taurog, 1998). It is strongly associated with the major histocompatibility class I (MHC I) HLA-B27 allele (Calin and Taurog, 1998). AS affects individuals in the prime of their life and is feared because of its potential to cause chronic pain and irreversible damage of tendons, ligaments, joints, and bones (Brewerton et al., 1973a; Brewerton et al., 1973b; Schlosstein et al., 1973). AS may occur alone or in association with another form of spondyloarthropathy such as reactive arthritis, psoriasis, psoriatic arthritis, enthesitis, ulcerative colitis, irritable bowel disease, or Crohn's disease, in which case it is classified as secondary AS.

Typically, the affected sites include the discovertebral, apophyseal, costovertebral, and costotransverse joints of the spine, and the paravertebral ligamentous structures. Inflammation of the entheses, which are sites of musculotendinous and ligamentous attachment to bones, is also prominent in this disease (Calin and Taurog, 1998). The site of enthesitis is known to be infiltrated by plasma cells, lymphocytes, and polymorphonuclear cells. The inflammatory process frequently results in gradual fibrous and bony ankylosis, (Ball, 1971; Khan, 1990).

Delayed diagnosis is common because symptoms are often attributed to more common back problems. A dramatic loss of flexibility in the lumbar spine is an early sign of AS. Other common symptoms include chronic pain and stiffness in the lower back which usually starts where the lower spine is joined to the pelvis, or hip. Although most symptoms begin in the lumbar and sacroiliac areas, they may involve the neck and upper back as well. Arthritis may also occur in the shoulder, hips and feet. Some patients have eye inflammation, and more severe cases must be observed for heart valve involvement.

The most frequent presentation is back pain, but disease can begin atypically in peripheral joints, especially in children and women, and rarely with acute iritis (anterior uveitis). Additional early symptoms and signs are diminished chest expansion from diffuse costovertebral involvement, low-grade fever, fatigue, anorexia, weight loss, and anemia. Recurrent back pain—often nocturnal and of varying intensity—is an eventual complaint, as is morning stiffness typically relieved by activity. A flexed or bent-over posture eases back pain and paraspinal muscle spasm; thus, some degree of kyphosis is common in untreated patients.

Systemic manifestations occur in 1/3 of patients. Recurrent, usually self-limited, acute iritis (anterior uveitis) rarely is protracted and severe enough to impair vision. Neurologic signs can occasionally result from compression radiculitis or sciatica, vertebral fracture or subluxation, and cauda equina syndrome (which consists of impotence, nocturnal urinary incontinence, diminished bladder and rectal sensation, and absence of ankle jerks). Cardiovascular manifestations can include aortic insufficiency, angina, pericarditis, and ECG conduction abnormalities. A rare pulmonary finding is upper lobe fibrosis, occasionally with cavitation that may be mistaken for TB and can be complicated by infection with *Aspergillus*.

AS is characterized by mild or moderate flares of active spondylitis alternating with periods of almost or totally inactive inflammation. Proper treatment in most patients results in

minimal or no disability and in full, productive lives despite back stiffness. Occasionally, the course is severe and progressive, resulting in pronounced incapacitating deformities. The prognosis is bleak for patients with refractory iritis and for the rare patient with secondary amyloidosis.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with ankylosing spondylitis.

N. Ulcerative Colitis

Ulcerative colitis is a disease that causes inflammation and sores, called ulcers, in the lining of the large intestine. The inflammation usually occurs in the rectum and lower part of the colon, but it may affect the entire colon. Ulcerative colitis rarely affects the small intestine except for the end section, called the terminal ileum. Ulcerative colitis may also be called colitis or proctitis. The inflammation makes the colon empty frequently, causing diarrhea. Ulcers form in places where the inflammation has killed the cells lining the colon; the ulcers bleed and produce pus.

Ulcerative colitis is an inflammatory bowel disease (IBD), the general name for diseases that cause inflammation in the small intestine and colon. Ulcerative colitis can be difficult to diagnose because its symptoms are similar to other intestinal disorders and to another type of IBD, Crohn's disease. Crohn's disease differs from ulcerative colitis because it causes inflammation deeper within the intestinal wall. Also, Crohn's disease usually occurs in the small intestine, although it can also occur in the mouth, esophagus, stomach, duodenum, large intestine, appendix, and anus.

Ulcerative colitis may occur in people of any age, but most often it starts between ages 15 and 30, or less frequently between ages 50 and 70. Children and adolescents sometimes develop the disease. Ulcerative colitis affects men and women equally and appears to run in some families. Theories about what causes ulcerative colitis abound, but none have been proven. The most popular theory is that the body's immune system reacts to a virus or a bacterium by causing ongoing inflammation in the intestinal wall. People with ulcerative colitis have abnormalities of the immune system, but doctors do not know whether these abnormalities are a cause or a result of the disease. Ulcerative colitis is not caused by emotional distress or sensitivity to certain foods or food products, but these factors may trigger symptoms in some people.

The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Patients also may experience fatigue, weight loss, loss of appetite, rectal bleeding, and loss of body fluids and nutrients. About half of patients have mild symptoms. Others suffer frequent fever, bloody diarrhea, nausea, and severe abdominal cramps. Ulcerative colitis may also cause problems such as arthritis, inflammation of the eye, liver disease (hepatitis, cirrhosis, and primary sclerosing cholangitis), osteoporosis, skin rashes, and anemia. No one knows for sure why problems occur outside the colon. Scientists think these complications may occur when the immune system triggers inflammation in other parts of the body. Some of these problems go away when the colitis is treated.

A thorough physical exam and a series of tests may be required to diagnose ulcerative colitis. Blood tests may be done to check for anemia, which could indicate bleeding in the colon or rectum. Blood tests may also uncover a high white blood cell count, which is a sign of inflammation somewhere in the body. By testing a stool sample, the doctor can detect bleeding or infection in the colon or rectum. The doctor may do a colonoscopy or sigmoidoscopy. For either test, the doctor inserts an endoscope—a long, flexible, lighted tube

connected to a computer and TV monitor—into the anus to see the inside of the colon and rectum. The doctor will be able to see any inflammation, bleeding, or ulcers on the colon wall. During the exam, the doctor may do a biopsy, which involves taking a sample of tissue from the lining of the colon to view with a microscope. A barium enema x ray of the colon may also be required. This procedure involves filling the colon with barium, a chalky white solution. The barium shows up white on x-ray film, allowing the doctor a clear view of the colon, including any ulcers or other abnormalities that might be there.

Treatment for ulcerative colitis depends on the seriousness of the disease. Most people are treated with medication. In severe cases, a patient may need surgery to remove the diseased colon. Surgery is the only cure for ulcerative colitis. Some people whose symptoms are triggered by certain foods are able to control the symptoms by avoiding foods that upset their intestines, like highly seasoned foods, raw fruits and vegetables, or milk sugar (lactose). Each person may experience ulcerative colitis differently, so treatment is adjusted for each individual. Emotional and psychological support is important. Some people have remissions—periods when the symptoms go away—that last for months or even years. However, most patients' symptoms eventually return. This changing pattern of the disease means one cannot always tell when a treatment has helped. Some people with ulcerative colitis may need medical care for some time, with regular doctor visits to monitor the condition.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with ulcerative colitis.

O. Crohn's Disease

Another disorder for which immunosuppression has been tried is Crohn's disease. Crohn's disease symptoms include intestinal inflammation and the development of intestinal stenosis and fistulas; neuropathy often accompanies these symptoms. Anti-inflammatory drugs, such as 5-aminosalicylates (e.g., mesalamine) or corticosteroids, are typically prescribed, but are not always effective (reviewed in Botoman et al., 1998). Immunosuppression with cyclosporine is sometimes beneficial for patients resistant to or intolerant of corticosteroids (Brynskov et al., 1989).

Efforts to develop diagnostic and treatment tools against Crohn's disease have focused on the central role of cytokines (Schreiber, 1998; van Hogezaand and Verspaget, 1998). Cytokines are small secreted proteins or factors (5 to 20 kD) that have specific effects on cell-to-cell interactions, intercellular communication, or the behavior of other cells. Cytokines are produced by lymphocytes, especially T_H1 and T_H2 lymphocytes, monocytes, intestinal macrophages, granulocytes, epithelial cells, and fibroblasts (reviewed in Rogler and Andus, 1998; Galley and Webster, 1996). Some cytokines are pro-inflammatory (e.g., $TNF-\alpha$, IL-1(α and β), IL-6, IL-8, IL-12, or leukemia inhibitory factor [LIF]); others are anti-inflammatory (e.g., IL-1 receptor antagonist, IL-4, IL-10, IL-11, and TGF- β). However, there may be overlap and functional redundancy in their effects under certain inflammatory conditions.

In active cases of Crohn's disease, elevated concentrations of $TNF-\alpha$ and IL-6 are secreted into the blood circulation, and $TNF-\alpha$, IL-1, IL-6, and IL-8 are produced in excess locally by mucosal cells (id.; Funakoshi et al., 1998). These cytokines can have far-ranging effects on physiological systems including bone development, hematopoiesis, and liver, thyroid, and neuropsychiatric function. Also, an imbalance of the IL-1 β /IL-1ra ratio, in favor of pro-inflammatory IL-1 β , has been

observed in patients with Crohn's disease (Rogler and Andus, 1998; Saiki et al., 1998; Dionne et al., 1998; but see Kuboyama, 1998). One study suggested that cytokine profiles in stool samples could be a useful diagnostic tool for Crohn's disease (Saiki et al., 1998).

Treatments that have been proposed for Crohn's disease include the use of various cytokine antagonists (e.g., IL-1ra), inhibitors (e.g., of IL-1 β converting enzyme and antioxidants) and anti-cytokine antibodies (Rogler and Andus, 1998; van Hogezaand and Verspaget, 1998; Reimund et al., 1998; Luger et al., 1998; McAlindon et al., 1998). In particular, monoclonal antibodies against TNF- α have been tried with some success in the treatment of Crohn's disease (Targan et al., 1997; Stack et al., 1997; van Dullemen et al., 1995). These compounds may be used in combination therapy with compounds of the present disclosure.

Another approach to the treatment of Crohn's disease has focused on at least partially eradicating the bacterial community that may be triggering the inflammatory response and replacing it with a non-pathogenic community. For example, U.S. Pat. No. 5,599,795 discloses a method for the prevention and treatment of Crohn's disease in human patients. Their method was directed to sterilizing the intestinal tract with at least one antibiotic and at least one anti-fungal agent to kill off the existing flora and replacing them with different, select, well-characterized bacteria taken from normal humans. Borody taught a method of treating Crohn's disease by at least partial removal of the existing intestinal microflora by lavage and replacement with a new bacterial community introduced by fecal inoculum from a disease-screened human donor or by a composition comprising *Bacteroides* and *Escherichia coli* species. (U.S. Pat. No. 5,443,826).

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with Crohn's disease.

P. Systemic Lupus Erythematosus

There has also been no known cause for autoimmune diseases such as systemic lupus erythematosus. Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by deposition in tissues of autoantibodies and immune complexes leading to tissue injury (Kotzin, 1996). In contrast to autoimmune diseases such as MS and type 1 diabetes mellitus, SLE potentially involves multiple organ systems directly, and its clinical manifestations are diverse and variable (reviewed by Kotzin and O'Dell, 1995). For example, some patients may demonstrate primarily skin rash and joint pain, show spontaneous remissions, and require little medication. At the other end of the spectrum are patients who demonstrate severe and progressive kidney involvement that requires therapy with high doses of steroids and cytotoxic drugs such as cyclophosphamide (Kotzin, 1996).

The serological hallmark of SLE, and the primary diagnostic test available, is elevated serum levels of IgG antibodies to constituents of the cell nucleus, such as double-stranded DNA (dsDNA), single-stranded DNA (ss-DNA), and chromatin. Among these autoantibodies, IgG anti-dsDNA antibodies play a major role in the development of lupus glomerulonephritis (GN) (Hahn and Tsao, 1993; Ohnishi et al., 1994). Glomerulonephritis is a serious condition in which the capillary walls of the kidney's blood purifying glomeruli become thickened by accretions on the epithelial side of glomerular basement membranes. The disease is often chronic and progressive and may lead to eventual renal failure.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with SLE.

Q. Irritable Bowel Syndrome

The compounds and methods of this invention may be used for treating patients with Irritable bowel syndrome (IBS). IBS is a functional disorder characterized by abdominal pain and altered bowel habits. This syndrome may begin in young adulthood and can be associated with significant disability. This syndrome is not a homogeneous disorder. Rather, subtypes of IBS have been described on the basis of the predominant symptom—diarrhea, constipation, or pain. In the absence of “alarm” symptoms, such as fever, weight loss, and gastrointestinal bleeding, a limited workup is needed. Once a diagnosis of IBS is made, an integrated treatment approach can effectively reduce the severity of symptoms. IBS is a common disorder, although its prevalence rates have varied. In general, IBS affects about 15% of US adults and occurs about three times more often in women than in men (Jailwala et al., 2000).

IBS accounts for between 2.4 million and 3.5 million visits to physicians each year. It not only is the most common condition seen by gastroenterologists but also is one of the most common gastrointestinal conditions seen by primary care physicians (Everhart et al., 1991; Sandler, 1990).

IBS is also a costly disorder. Compared with persons who do not have bowel symptoms, persons with IBS miss three times as many workdays and are more likely to report being too sick to work (Drossman et al., 1993; Drossman et al., 1997). Moreover, those with IBS incur hundreds of dollars more in medical charges than persons without bowel disorders (Talley et al., 1995).

No specific abnormality accounts for the exacerbations and remissions of abdominal pain and altered bowel habits experienced by patients with IBS. The evolving theory of IBS suggests dysregulation at multiple levels of the brain-gut axis. Dysmotility, visceral hypersensitivity, abnormal modulation of the central nervous system (CNS), and infection have all been implicated. In addition, psychosocial factors play an important modifying role. Abnormal intestinal motility has long been considered a factor in the pathogenesis of IBS. Transit time through the small intestine after a meal has been shown to be shorter in patients with diarrhea-predominant IBS than in patients who have the constipation-predominant or pain-predominant subtype (Cann et al., 1983).

In studies of the small intestine during fasting, the presence of both discrete, clustered contractions and prolonged, propagated contractions has been reported in patients with IBS (Kellow and Phillips, 1987). They also experience pain with irregular contractions more often than healthy persons (Kellow and Phillips, 1987; Horwitz and Fisher, 2001).

These motility findings do not account for the entire symptom complex in patients with IBS; in fact, most of these patients do not have demonstrable abnormalities (Rothstein, 2000). Patients with IBS have increased sensitivity to visceral pain. Studies involving balloon distention of the rectosigmoid colon have shown that patients with IBS experience pain and bloating at pressures and volumes much lower than control subjects (Whitehead et al., 1990). These patients maintain normal perception of somatic stimuli.

Multiple theories have been proposed to explain this phenomenon. For example, receptors in the viscera may have increased sensitivity in response to distention or intraluminal contents. Neurons in the dorsal horn of the spinal cord may have increased excitability. In addition, alteration in CNS processing of sensations may be involved (Drossman et al., 1997). Functional magnetic resonance imaging studies have

recently shown that compared with control subjects, patients with IBS have increased activation of the anterior cingulate cortex, an important pain center, in response to a painful rectal stimulus (Mertz et al., 2000).

Increasingly, evidence suggests a relationship between infectious enteritis and subsequent development of IBS. Inflammatory cytokines may play a role. In a survey of patients with a history of confirmed bacterial gastroenteritis (Neal et al., 1997), 25% reported persistent alteration of bowel habits. Persistence of symptoms may be due to psychological stress at the time of acute infection (Gwee et al., 1999).

Recent data suggest that bacterial overgrowth in the small intestine may have a role in IBS symptoms. In one study (Pimentel et al., 2000), 157 (78%) of 202 IBS patients referred for hydrogen breath testing had test findings that were positive for bacterial overgrowth. Of the 47 subjects who had follow-up testing, 25 (53%) reported improvement in symptoms (i.e., abdominal pain and diarrhea) with antibiotic treatment.

IBS may present with a range of symptoms. However, abdominal pain and altered bowel habits remain the primary features. Abdominal discomfort is often described as crampy in nature and located in the left lower quadrant, although the severity and location can differ greatly. Patients may report diarrhea, constipation, or alternating episodes of diarrhea and constipation. Diarrheal symptoms are typically described as small-volume, loose stools, and stool is sometimes accompanied by mucus discharge. Patients also may report bloating, fecal urgency, incomplete evacuation, and abdominal distention. Upper gastrointestinal symptoms, such as gastroesophageal reflux, dyspepsia, or nausea, may also be present (Lynn and Friedman, 1993).

Persistence of symptoms is not an indication for further testing; it is a characteristic of IBS and is itself an expected symptom of the syndrome. More extensive diagnostic evaluation is indicated in patients whose symptoms are worsening or changing. Indications for further testing also include presence of alarm symptoms, onset of symptoms after age 50, and a family history of colon cancer. Tests may include colonoscopy, computed tomography of the abdomen and pelvis, and barium studies of the small or large intestine.

R. Sjögren's Syndrome

The compounds and methods of this invention may be used for treating patients with SS. Primary Sjögren's syndrome (SS) is a chronic, slowly progressive, systemic autoimmune disease, which affects predominantly middle-aged women (female-to-male ratio 9:1), although it can be seen in all ages including childhood (Jonsson et al., 2002). It is characterized by lymphocytic infiltration and destruction of the exocrine glands, which are infiltrated by mononuclear cells including CD4+, CD8+ lymphocytes and B-cells (Jonsson et al., 2002). In addition, extraglandular (systemic) manifestations are seen in one-third of patients (Jonsson et al., 2001).

The glandular lymphocytic infiltration is a progressive feature (Jonsson et al., 1993), which, when extensive, may replace large portions of the organs. Interestingly, the glandular infiltrates in some patients closely resemble ectopic lymphoid microstructures in the salivary glands (denoted as ectopic germinal centers) (Salomonsson et al., 2002; Xanthou et al., 2001). In SS, ectopic GCs are defined as T and B cell aggregates of proliferating cells with a network of follicular dendritic cells and activated endothelial cells. These GC-like structures formed within the target tissue also portray functional properties with production of autoantibodies (anti-Ro/SSA and anti-La/SSB) (Salomonsson and Jonsson, 2003).

In other systemic autoimmune diseases, such as RA, factors critical for ectopic GCs have been identified. Rheumatoid synovial tissues with GCs were shown to produce chemokines CXCL13, CCL21 and lymphotoxin (LT)- β (detected on follicular center and mantle zone B cells). Multivariate regression analysis of these analytes identified CXCL13 and LT- β as the solitary cytokines predicting GCs in rheumatoid synovitis (Weyand and Goronzy, 2003). Recently CXCL13 and CXCR5 in salivary glands has been shown to play an essential role in the inflammatory process by recruiting B and T cells, therefore contributing to lymphoid neogenesis and ectopic GC formation in SS (Salomonsson et al., 2002).

S. Psoriasis

The compounds and methods of this invention may be used for treating patients with psoriasis. Psoriasis is a chronic skin disease of scaling and inflammation that affects 2 to 2.6 percent of the United States population, or between 5.8 and 7.5 million people. Although the disease occurs in all age groups, it primarily affects adults. It appears about equally in males and females. Psoriasis occurs when skin cells quickly rise from their origin below the surface of the skin and pile up on the surface before they have a chance to mature. Usually this movement (also called turnover) takes about a month, but in psoriasis it may occur in only a few days. In its typical form, psoriasis results in patches of thick, red (inflamed) skin covered with silvery scales. These patches, which are sometimes referred to as plaques, usually itch or feel sore. They most often occur on the elbows, knees, other parts of the legs, scalp, lower back, face, palms, and soles of the feet, but they can occur on skin anywhere on the body. The disease may also affect the fingernails, the toenails, and the soft tissues of the genitals and inside the mouth. While it is not unusual for the skin around affected joints to crack, approximately 1 million people with psoriasis experience joint inflammation that produces symptoms of arthritis. This condition is called psoriatic arthritis.

Psoriasis is a skin disorder driven by the immune system, especially involving a type of white blood cell called a T cell. Normally, T cells help protect the body against infection and disease. In the case of psoriasis, T cells are put into action by mistake and become so active that they trigger other immune responses, which lead to inflammation and to rapid turnover of skin cells. In about one-third of the cases, there is a family history of psoriasis. Researchers have studied a large number of families affected by psoriasis and identified genes linked to the disease. People with psoriasis may notice that there are times when their skin worsens, then improves. Conditions that may cause flareups include infections, stress, and changes in climate that dry the skin. Also, certain medicines, including lithium and beta blockers, which are prescribed for high blood pressure, may trigger an outbreak or worsen the disease.

T. Infectious Diseases

Compounds of the present disclosure may be useful in the treatment of infectious diseases, including viral and bacterial infections. As noted above, such infections may be associated with severe localized or systemic inflammatory responses. For example, influenza may cause severe inflammation of the lung and bacterial infection can cause the systemic hyperinflammatory response, including the excessive production of multiple inflammatory cytokines, that is the hallmark of sepsis. In addition, compounds of the invention may be useful in directly inhibiting the replication of viral pathogens. Previous studies have demonstrated that related compounds such as CDDO can inhibit the replication of HIV in macrophages (Vazquez et al., 2005). Other studies have indicated that inhibition of NF-kappa B signaling may inhibit influenza virus

replication, and that cyclopentenone prostaglandins may inhibit viral replication (e.g., Mazur et al., 2007; Pica et al., 2000).

V. Pharmaceutical Formulations and Routes of Administration

The compounds of the present disclosure may be administered by a variety of methods, e.g., orally or by injection (e.g. subcutaneous, intravenous, intraperitoneal, etc.). Depending on the route of administration, the active compounds may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. They may also be administered by continuous perfusion/infusion of a disease or wound site.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a patient in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., 1984).

The therapeutic compound may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile carrier which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-

drying which yields a powder of the active ingredient (i.e., the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of a selected condition in a patient.

The therapeutic compound may also be administered topically to the skin, eye, or mucosa. Alternatively, if local delivery to the lungs is desired the therapeutic compound may be administered by inhalation in a dry-powder or aerosol formulation.

Active compounds are administered at a therapeutically effective dosage sufficient to treat a condition associated with a condition in a patient. A "therapeutically effective amount" preferably reduces the amount of symptoms of the condition in the infected patient by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. For example, the efficacy of a compound can be evaluated in an animal model system that may be predictive of efficacy in treating the disease in humans, such as the model systems shown in the examples and drawings.

The actual dosage amount of a compound of the present disclosure or composition comprising a compound of the present disclosure administered to a subject may be determined by physical and physiological factors such as age, sex, body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiosyncrasy of the subject and on the route of administration. These factors may be determined by a skilled artisan. The practitioner responsible for administration will typically determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. The dosage may be adjusted by the individual physician in the event of any complication.

An effective amount typically will vary from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 100 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, from about 10.0 mg/kg to about 150 mg/kg in one or more dose administrations daily, for one or several days (depending of course of the mode of administration and the factors discussed above). Other suit-

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able dose ranges include 1 mg to 10000 mg per day, 100 mg to 10000 mg per day, 500 mg to 10000 mg per day, and 500 mg to 1000 mg per day. In some particular embodiments, the amount is less than 10,000 mg per day with a range of 750 mg to 9000 mg per day.

The effective amount may be less than 1 mg/kg/day, less than 500 mg/kg/day, less than 250 mg/kg/day, less than 100 mg/kg/day, less than 50 mg/kg/day, less than 25 mg/kg/day or less than 10 mg/kg/day. It may alternatively be in the range of 1 mg/kg/day to 200 mg/kg/day. For example, regarding treatment of diabetic patients, the unit dosage may be an amount that reduces blood glucose by at least 40% as compared to an untreated subject. In another embodiment, the unit dosage is an amount that reduces blood glucose to a level that is $\pm 10\%$ of the blood glucose level of a non-diabetic subject.

In other non-limiting examples, a dose may also comprise from about 1 micro-gram/kg/body weight, about 5 micro-gram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500 microgram/kg/body weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, to about 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers listed herein, a range of about 5 mg/kg/body weight to about 100 mg/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, etc., can be administered, based on the numbers described above.

In certain embodiments, a pharmaceutical composition of the present disclosure may comprise, for example, at least about 0.1% of a compound of the present disclosure. In other embodiments, the compound of the present disclosure may comprise between about 2% to about 75% of the weight of the unit, or between about 25% to about 60%, for example, and any range derivable therein.

Single or multiple doses of the agents are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the agent is administered once a day.

The agent(s) may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks there-between. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months, etc. In other embodiments, the invention provides that the agent(s) may be taken orally and that the timing of which is or is not dependent upon food intake. Thus, for example, the agent can be taken every morning and/or every evening, regardless of when the subject has eaten or will eat.

VI. Combination Therapy

In addition to being used as a monotherapy, the compounds of the present disclosure may also find use in combination

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therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, at the same time, wherein one composition includes a compound of the present disclosure, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

Various combinations may be employed, such as when a compound of the present disclosure is "A" and "B" represents a secondary agent, non-limiting examples of which are described below:

A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B
B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A
B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

Administration of the compounds of the present disclosure to a patient will follow general protocols for the administration of pharmaceuticals, taking into account the toxicity, if any, of the drug. It is expected that the treatment cycles would be repeated as necessary.

Beta interferons may be suitable secondary agents. These are medications derived from human cytokines which help regulate the immune system. They include interferon β -1b and interferon β -1a. Betaseron has been approved by the FDA for relapsing forms of secondary progressive MS. Furthermore, the FDA has approved the use of several β -interferons as treatments for people who have experienced a single attack that suggests multiple sclerosis, and who may be at risk of future attacks and developing definite MS. For example, risk of MS may be suggested when an MRI scan of the brain shows lesions that predict a high risk of conversion to definite MS.

Glatiramer acetate is a further example of a secondary agent that may be used in a combination treatment. Glatiramer is presently used to treat relapsing remitting MS. It is made of four amino acids that are found in myelin. This drug is reported to stimulate T cells in the body's immune system to change from harmful, pro-inflammatory agents to beneficial, anti-inflammatory agents that work to reduce inflammation at lesion sites.

Another potential secondary agent is mitoxantrone, a chemotherapy drug used for many cancers. This drug is also FDA-approved for treatment of aggressive forms of relapsing remitting MS, as well as certain forms of progressive MS. It is given intravenously, typically every three months. This medication is effective, but is limited by cardiac toxicity. Novantrone has been approved by the FDA for secondary progressive, progressive-relapsing, and worsening relapsing-remitting MS.

Another potential secondary agent is natalizumab. In general, natalizumab works by blocking the attachment of immune cells to brain blood vessels, which is a necessary step for immune cells to cross into the brain, thus reducing the immune cells' inflammatory action on brain neurons. Natalizumab has been shown to significantly reduce the frequency of attacks in people with relapsing MS.

In the case of relapsing remitting MS, patients may be given intravenous corticosteroids, such as methylprednisolone, as a secondary agent, to end the attack sooner and leave fewer lasting deficits.

Other common drugs for MS that may be used in combination with compounds of the present disclosure include immunosuppressive drugs such as azathioprine, cladribine, and cyclophosphamide.

It is contemplated that other anti-inflammatory agents may be used in conjunction with the treatments of the current invention. Other COX inhibitors may be used, including aryl-carboxylic acids (salicylic acid, acetylsalicylic acid, diflunisal, choline magnesium trisalicylate, salicylate, benorlylate, flufenamic acid, mefenamic acid, meclofenamic acid and triflumic acid), arylalkanoic acids (diclofenac, fenclufenac, alclofenac, fentiazac, ibuprofen, flurbiprofen, ketoprofen, naproxen, fenoprofen, fenbufen, suprofen, indoprofen, tiaprofenic acid, benoxaprofen, piroprofen, tolmetin, zomepirac, clopinac, indomethacin and sulindac) and enolic acids (phenylbutazone, oxyphenbutazone, azapropazone, feprazone, piroxicam, and isoxicam. See, e.g., U.S. Pat. No. 6,025,395.

Histamine H2 receptor blocking agents may also be used in conjunction with the compounds of the current invention, including cimetidine, ranitidine, famotidine and nizatidine.

Treatment with acetylcholinesterase inhibitors such as tacrine, donepezil, metrifonate and rivastigmine for the treatment of Alzheimer's and other disease in conjunction with the compounds of the present disclosure is contemplated. Other acetylcholinesterase inhibitors may be developed which may be used once approved include rivastigmine and metrifonate. Acetylcholinesterase inhibitors increase the amount of neurotransmitter acetylcholine at the nerve terminal by decreasing its breakdown by the enzyme cholinesterase.

MAO-B inhibitors such as selegiline may be used in conjunction with the compounds of the current invention. Selegiline is used for Parkinson's disease and irreversibly inhibits monoamine oxidase type B (MAO-B). Monoamine oxidase is an enzyme that inactivates the monoamine neurotransmitters norepinephrine, serotonin and dopamine.

Dietary and nutritional supplements with reported benefits for treatment or prevention of Parkinson's, Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel disease, and all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide (NO) or prostaglandins, such as acetyl-L-carnitine, octacosanol, evening primrose oil, vitamin B6, tyrosine, phenylalanine, vitamin C, L-dopa, or a combination of several antioxidants may be used in conjunction with the compounds of the current invention.

For the treatment or prevention of cancer, compounds of the invention may be combined with one or more of the following: radiation, chemotherapy agents (e.g., cytotoxic agents such as anthracyclines, vincristine, vinblastin, microtubule-targeting agents such as paclitaxel and docetaxel, 5-FU and related agents, cisplatin and other platinum-containing compounds, irinotecan and topotecan, gemcitabine, temozolomide, etc.), targeted therapies (e.g., imatinib, bortezomib, bevacizumab, rituximab), or vaccine therapies designed to promote an enhanced immune response targeting cancer cells.

For the treatment or prevention of autoimmune disease, compounds of the invention may be combined with one or more of the following: corticosteroids, methotrexate, anti-TNF antibodies, other TNF-targeting protein therapies, and NSAIDs. For the treatment or prevention of cardiovascular diseases, compounds of the invention may be combined with antithrombotic therapies, anticholesterol therapies such as statins (e.g., atorvastatin), and surgical interventions such as

stenting or coronary artery bypass grafting. For the treatment of osteoporosis, compounds of the invention may be combined with antiresorptive agents such as bisphosphonates or anabolic therapies such as teriparatide or parathyroid hormone. For the treatment of neuropsychiatric conditions, compounds of the invention may be combined with antidepressants (e.g., imipramine or SSRIs such as fluoxetine), antipsychotic agents (e.g., olanzapine, sertindole, risperidone), mood stabilizers (e.g., lithium, valproate semisodium), or other standard agents such as anxiolytic agents. For the treatment of neurological disorders, compounds of the invention may be combined with anticonvulsant agents (e.g., valproate semisodium, gabapentin, phenytoin, carbamazepine, and topiramate), antithrombotic agents (e.g., tissue plasminogen activator), or analgesics (e.g., opioids, sodium channel blockers, and other antinociceptive agents).

VII. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Methods and Materials

Nitric Oxide Production and Cell Viability.

RAW264.7 macrophages were pre-treated with DMSO or drugs for 2 hours, then treated with recombinant mouse IFN γ (Sigma) for 24 hours. NO concentration in media was determined using the Griess reagent system (Promega). Cell viability was determined using WST-1 reagent (Roche).

iNOS Induction qPCR.

RAW264.7 mouse macrophage cells were pre-treated for 2 hours with compounds at the indicated concentrations and subsequently stimulated with 10 ng/ml IFN γ for an additional 2 hours. mRNA levels of iNOS were quantified by qPCR and are shown relative to the vehicle-treated IFN γ -stimulated sample which was normalized to a value of 1. Values are averages of duplicate PCR reactions, each with triplicate wells.

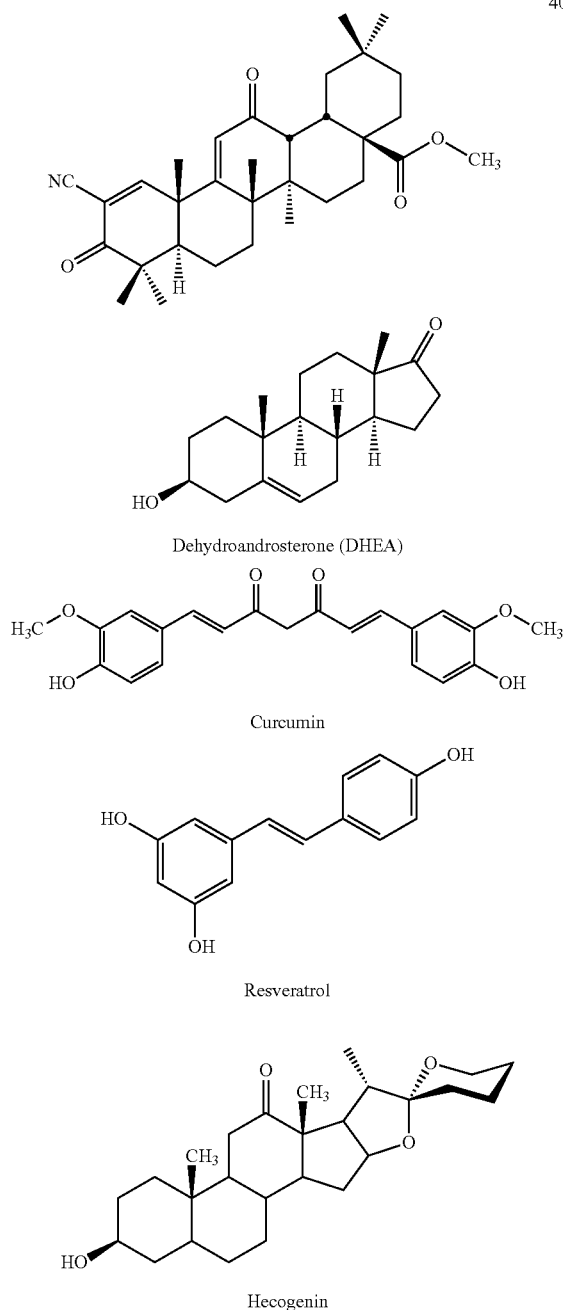
iNOS Induction Western Blot.

RAW264.7 cells were pre-treated for 2 hours with indicated compounds and subsequently stimulated with 10 ng/ml IFN γ for an additional 24 hours. iNOS protein levels were assayed by immunoblotting. Actin was used as a loading control.

Comparison Compounds.

In some of the experiments (e.g., FIGS. 17, 18), the compounds of this invention were compared with other synthetic triterpenoids and natural products, such as those shown here:

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Compound 402 can be prepared according to the methods taught by Honda et al. (1998), Honda et al. (2000b), Honda et al. (2002), Yates et al. (2007), and U.S. Pat. Nos. 6,326,507 and 6,974,801, which are incorporated herein by reference.

Example 2

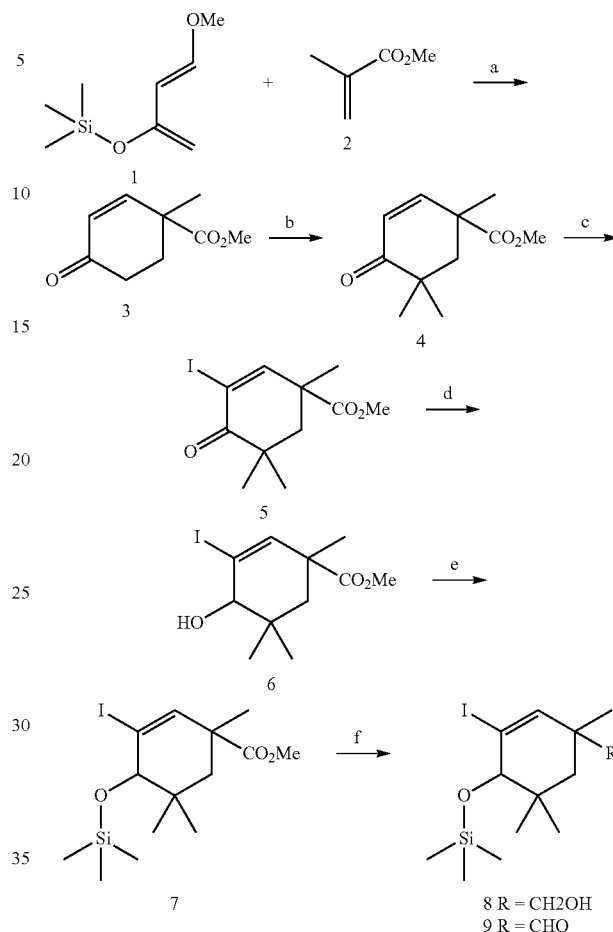
Synthesis of Certain Natural Products Including an Anti-Inflammatory Pharmacore

Curcumin analogs C0008, C0009 and C0010 were synthesized as described in Schemes 1-3.

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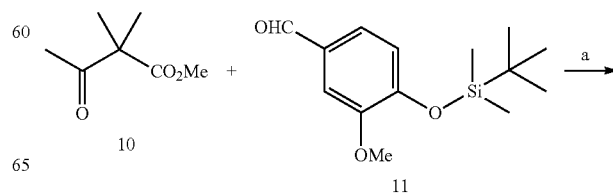
Scheme 1

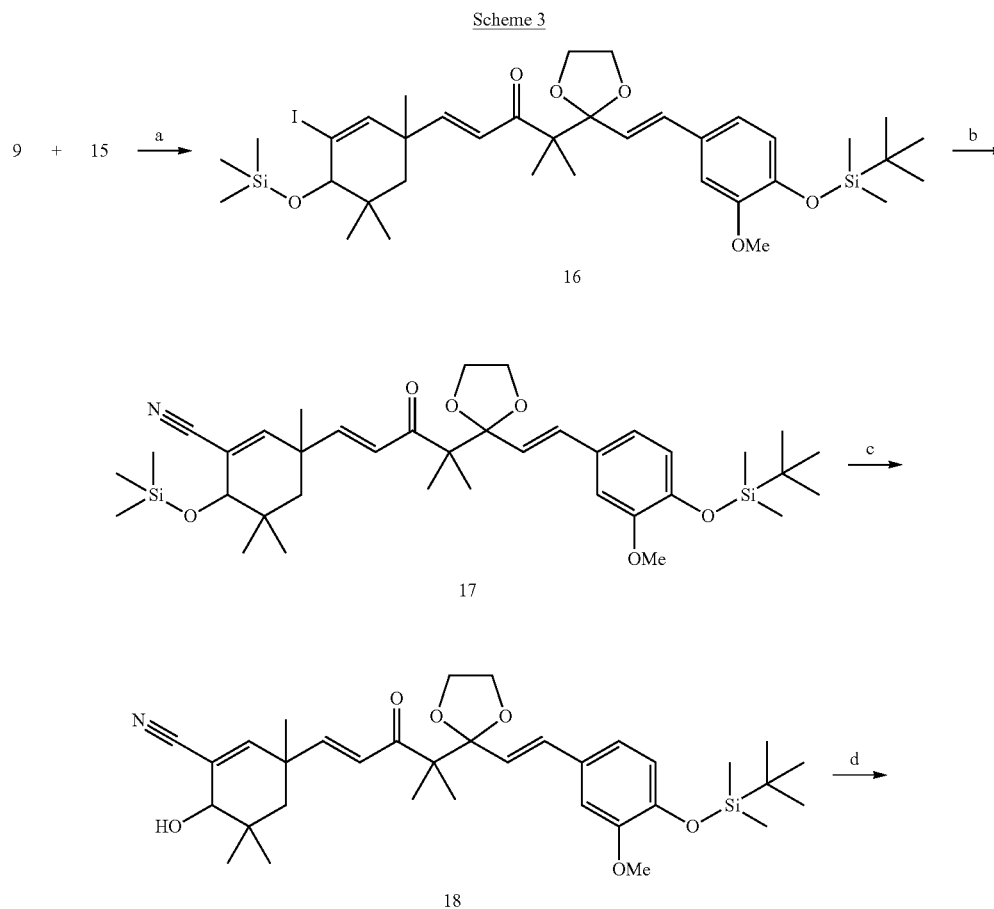
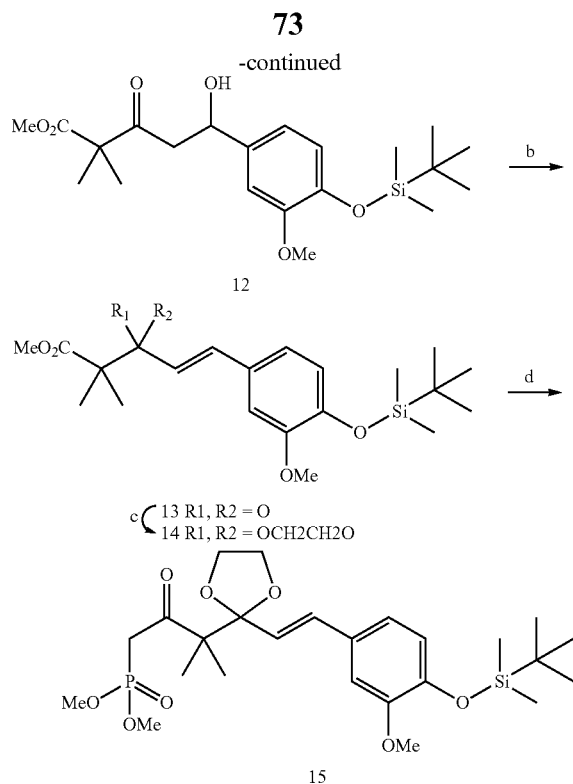


Reagents and conditions for Scheme 1: (a) 130° C., 16 h, 68%; (b) (i) LHMDs, MeI, -78° C. to rt, 3 h; (ii) LHMDs, MeI, -78° C. to rt, 3 h, 71%; (c) I₂, 50° C., 24 h, 95%; (d) NaBH₄, CeCl₃·7H₂O, 0° C., 1.5 h, 80%; (e) TMSCl, imidazole, 0° C., 1 h, 95%; (f) (i) DIBAL-H, -78° C., 1 h; (ii) DMP, rt, 20 min, 85%.

As shown in Scheme 1, compound 3 (68%) was prepared by Diels-Alder reaction of compound 1 and 2 using a protocol modified from the method reported by Danishefsky et al., 1979. After introduction of the gem-dimethyl group to give compound 4 (71% yield), vinyl iodide 5 (95% yield) was produced. The enone was reduced to allylic alcohol 6 and protected to give TMS ether 7 (80% for two steps). The methyl ester 7 was then transformed to aldehyde 9 in two steps (91% yield).

Scheme 2

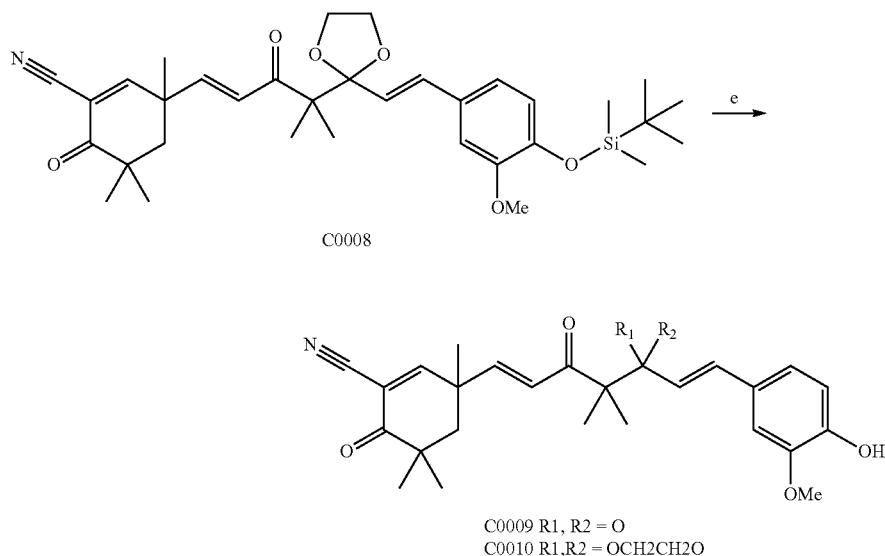




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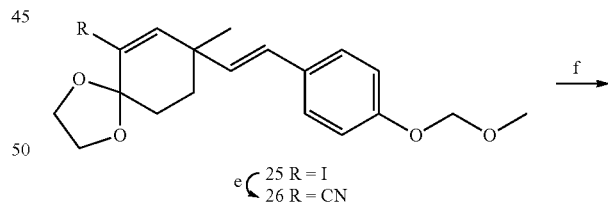
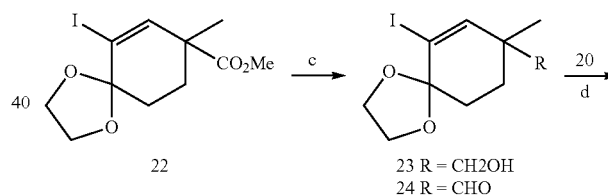
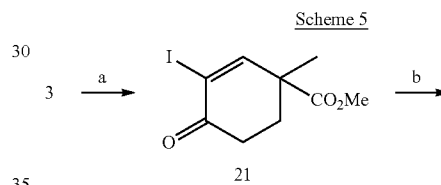
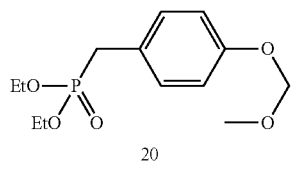
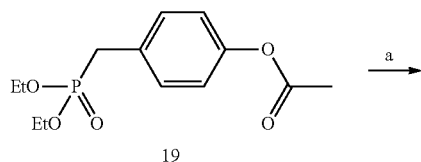
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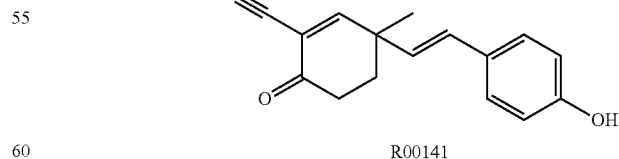
Reagents and conditions for Scheme 3: (a) DIPEA, LiCl, 60° C., 20 h, 28%; (b) Zn(CN)₂, Pd(PPh₃)₄, 80° C., 20 min, 68%; (c) TsOH, rt, 30 min, 99%; (d) DMP, rt, 1 h, 77%; (e) 6 N HCl (aq), rt, 14 h, 88% (for C0009); TBAF, rt, 10 min, 63% (for C0010).

Scheme 4



Reagents and conditions for Scheme 4: (a) (i) K₂CO₃, rt, 2 h; (ii) MOMCl, DIPEA, rt, 14 h, 94%.

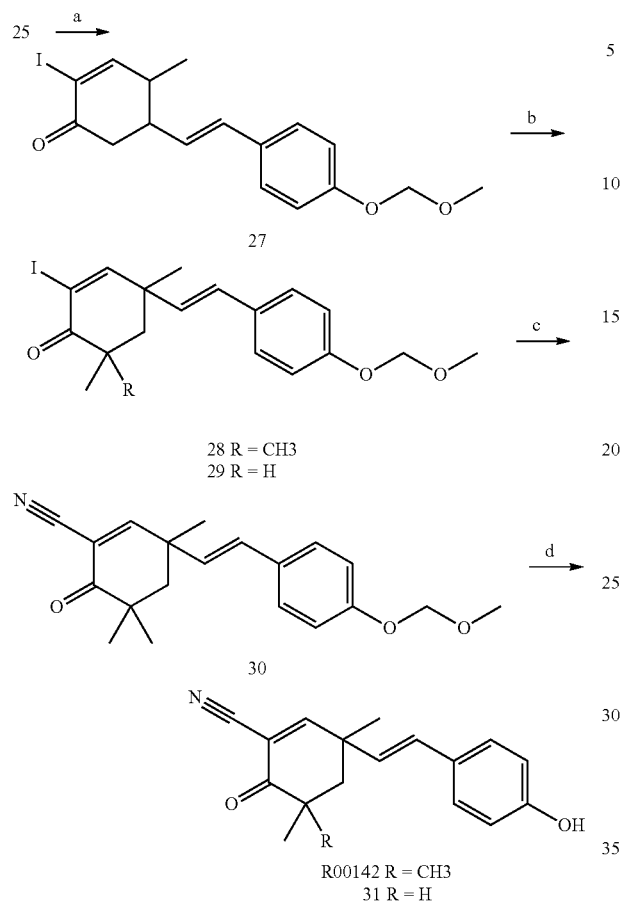
The synthesis of Resveratrol analog R00141 is summarized in Scheme 4 and Scheme 5, below. Starting material 3 was first treated with I₂/Py to produce the vinyl iodide 21 (74%). The vinyl iodide was then protected to give ketal 22, which was used directly in the next reaction. Ketal 22 was transformed to aldehyde 24 in two steps and high yield (91%). Aldehyde 24 was reacted with diethyl phosphite 20 under basic conditions to produce compound 25 in 89% yield. The vinyl iodide 25 was treated with Zn(CN)₂ and catalytic amount of Pd(PPh₃)₄, and cyanide 26 was obtained in 62% yield. The ketal and MOM protection groups were removed in one step using TsOH to give R00141 (87%).



Reagents and conditions for Scheme 5: (a) I₂, rt, 16 h, 74%; (b) ethylene glycol, 110° C., 3 h; (c) (i) DIBAL-H, -78° C., 1 h; (ii) DMP, rt, 20 min, 91%; (d) t-BuOK, 0° C. to rt, 2 h, 89%; (e) Zn(CN)₂, Pd(PPh₃)₄, 80° C., 20 min, 62%; (f) TsOH, rt, 2 min, 87%.

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Scheme 6

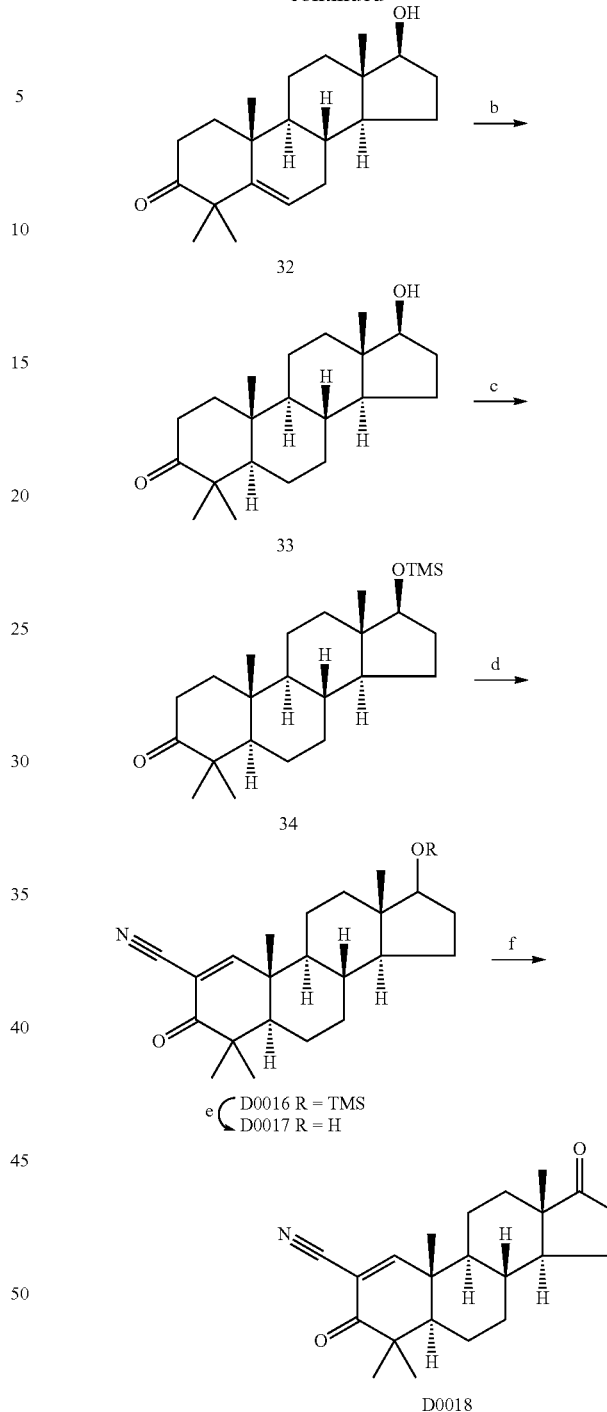


Reagents and conditions for Scheme 6: (a) TsOH, rt, 89%; (b) (i) LHMDs, MeI, -78° C. to rt, 3 h; (ii) LHMDs, MeI, -78° C. to rt, 3 h, 48%; (c) Zn(CN)₂, Pd(PPh₃)₄, 80° C., 20 min, 42%; (f) TsOH, rt, 2 min, 93%.

R00142 was synthesized from compound 25 (Scheme 6). Compound 25 was treated with TsOH, selectively removing the ketal group, to give enone 27 (89%). The gem-dimethyl group was then introduced using LHMDs/MeI. From the reaction mixture, compound 28 was isolated in 48% yield. A mixture of compound 28 and 29 (14%) was also obtained. Using the same protocol described for the synthesis of R00141, R00142 was obtained from compound 28 in 39% yield. From the mixture of compound 28 and 29, a mixture of R00142 and compound 31 (named as R00142-1) were obtained.

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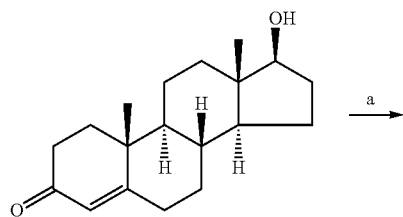
-continued



Reagents and conditions for Scheme 7: (a) t-BuOK, MeI, rt, 4 h, 62%; (b) H₂, 10% Pd/C, rt, 16 h, 38%; (c) Imidazole, TMSCl, rt, 1 h, 84%; (d) (i) LDA, TsCN, -78° C. to 0° C., 1 h; (ii) DDQ, 80° C., 20 min, 50%; (e) TsOH, rt, 5 min, 95%; (f) DMP, rt, 2 h, 79%.

DHEA analog D0016 was synthesized from testosterone (Scheme 7). Testosterone was treated with t-BuOK/MeI (Cao et al., 2007) to introduce the gem-dimethyl group at the 4-position, giving compound 32 in 62% yield. Compound 32 was then hydrogenated to get 33 (38%). After the 17-hydroxyl group was protected (84% yield), compound 34 was treated

Scheme 7

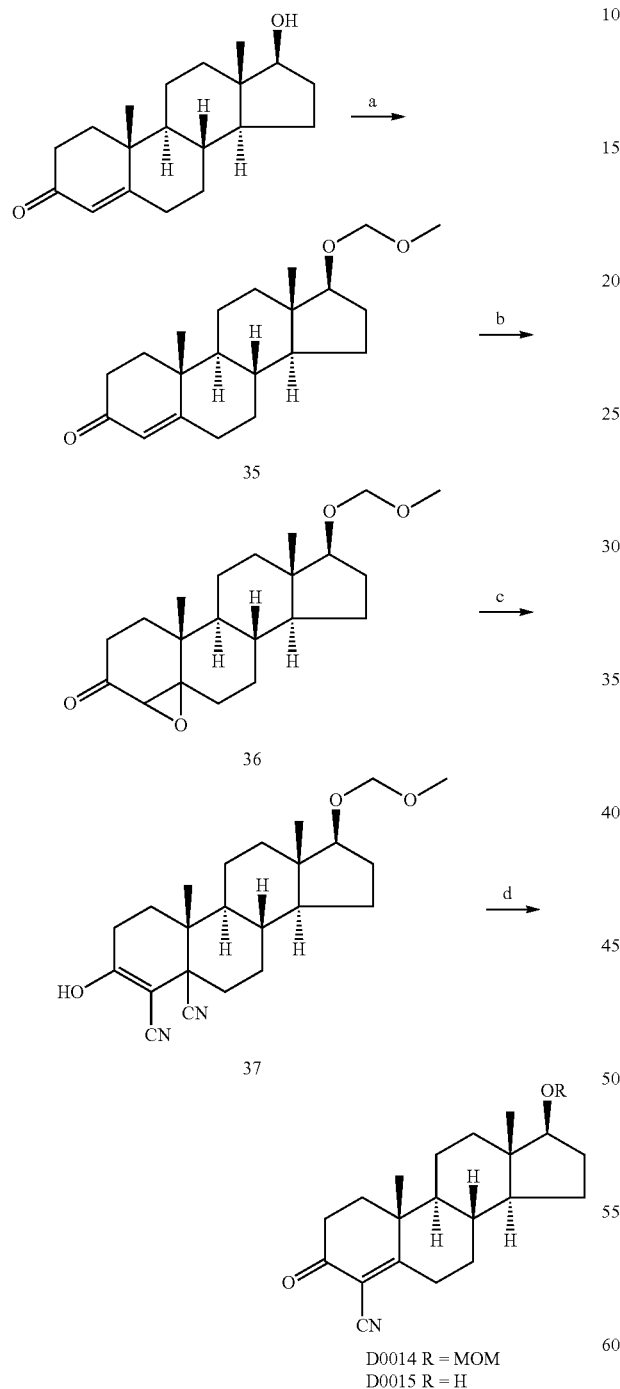


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with LDA/TsCN (Kahne and Collum, 1981), followed by DDQ oxidation to give target compound D0016 in 50% yield.

D0017 and D0018 were synthesized from D0016 (Scheme 7). D0016 was treated with TsOH to afford D0017 in 95% yield. D0017 was oxidized with Dess-Martin periodinane to give compound D0018 (79%).

Scheme 8

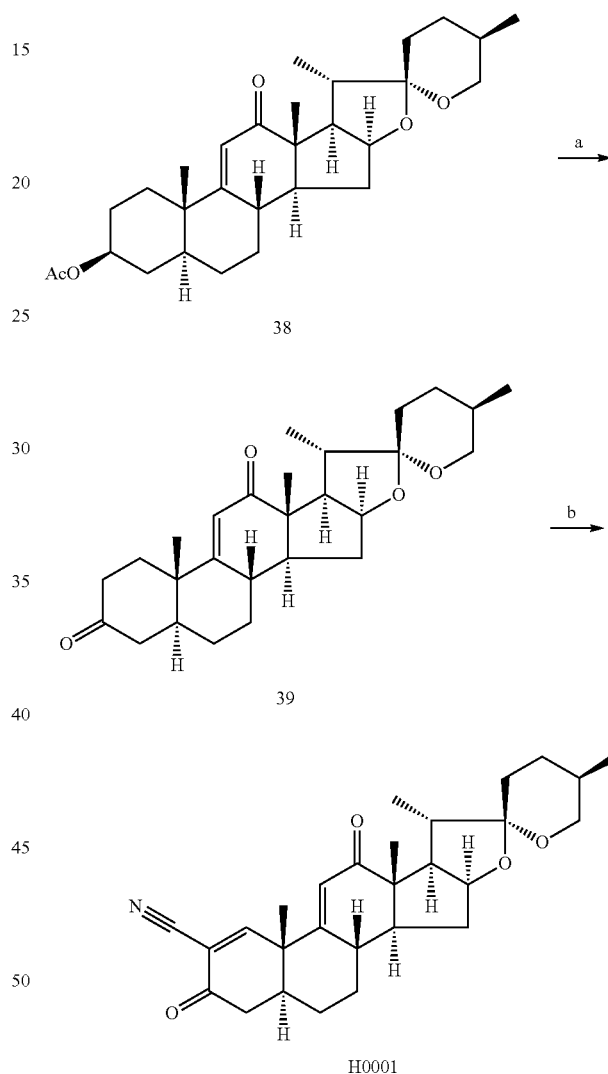


Reagents and conditions for Scheme 8: (a) MOMCl, DIPEA, DMAP, rt, 14 h, 98%; (b) H₂O₂, NaOH, 4° C., 14 h, 71%; (c) NaCN, EtOH, 80° C., 24 h; (d) 210° C., 40 min, 23% of D0014 (from 36) and 23% of D0015 (from 36).

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Compound D0014 was prepared from compound 35 using the protocol reported by Rasmussen et al., 1986 (Scheme 8). Compound 35 (produced from testosterone in 98% yield) was treated with alkaline hydrogen peroxide to give a mixture of epoxide epimers. The mixture was converted to base-soluble dicyano compound 37, which was used in the next step directly. Gentle pyrolysis of compound 37 afforded the corresponding 4-cyano-steroids D0014 (23%) and D0015 (23%).

Scheme 9



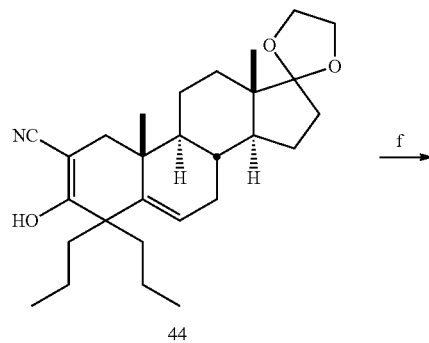
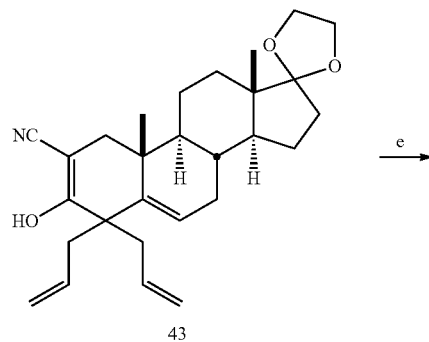
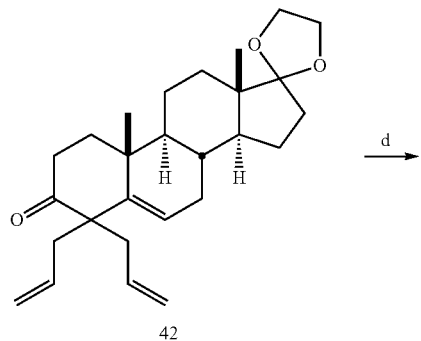
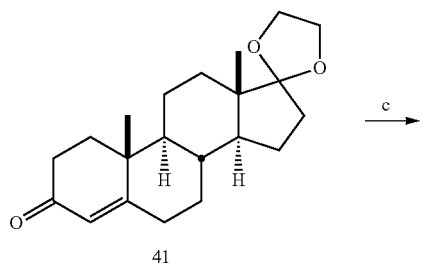
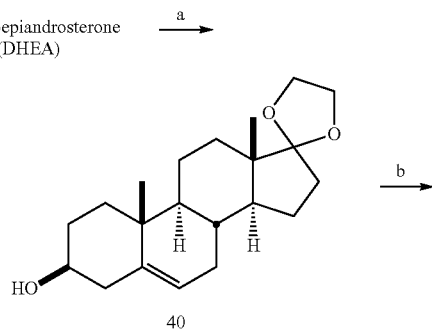
Reagents and conditions for Scheme 9: (a) (i) K_2CO_3 , rt, 4 h; (ii) PCC, NaOAc, rt, 3 h, 95%; (b) (i) LDA, TsCN, -78°C . to 0°C ., 1 h; (ii) DDQ, 80°C ., 20 min, 37%.

Hecogenin analog H0001 was synthesized from compound 38 (Scheme 9). Compound 38 was prepared from hecogenin acetate using the reported procedure (Barton et al., 1980). Acetate 38 was treated with base, followed by PCC oxidation to give ketone 39 in 95% yield. 39 was then reacted with LDA/TsCN (Kahne and Collum, 1981), followed by DDQ oxidation to give target compound H0001 (37%).

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Scheme 10:

Dehydroepiandrosterone
(DHEA)

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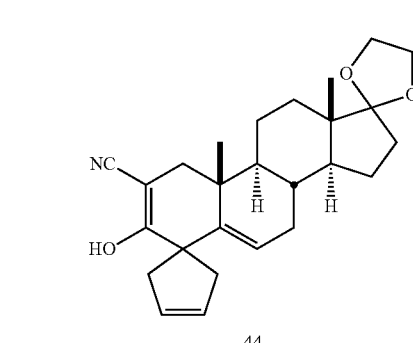
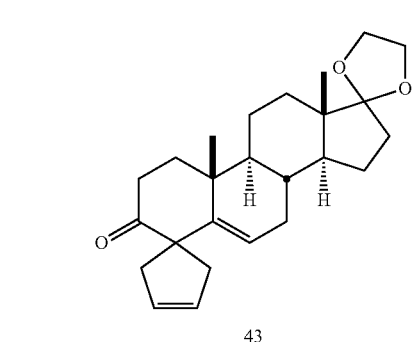
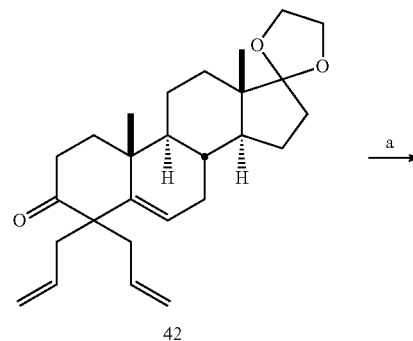
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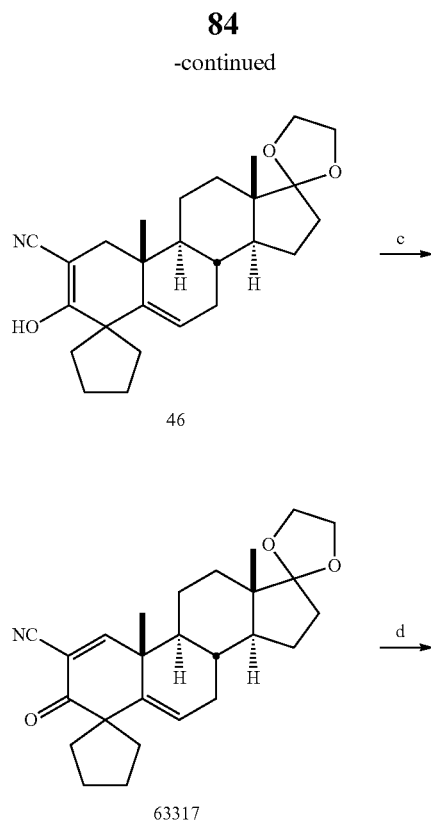
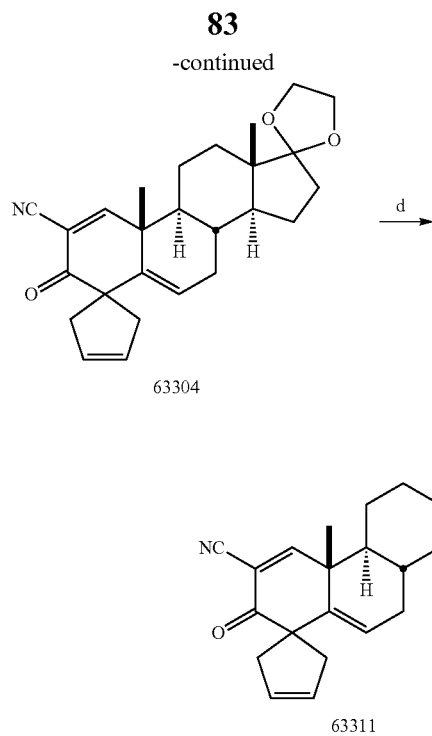
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Reagents and conditions for Scheme 10: (a) ethylene glycol, CSA, cyclohexane, Dean-Stark, reflux, 20 h, 99%; (b) 3-methyl-2-butanone, Al(Oi-Pr)₃, toluene, reflux, 4 h, 72%; (c) KOt-Bu (1 M in THF), t-BuOH, allyl bromide, rt, 2 h, 73%; (d) LDA, THF, -78° C., 30 min; TsCN, -78° C., 30 min, 57%; (e) H₂ (1 atm), 10% Pd/C, THF, 2 h, 100%; (f) (i) DDQ, benzene, 80° C., 3 h; (ii) 1 N HCl (aq), THF, rt, 2 h, 10%.

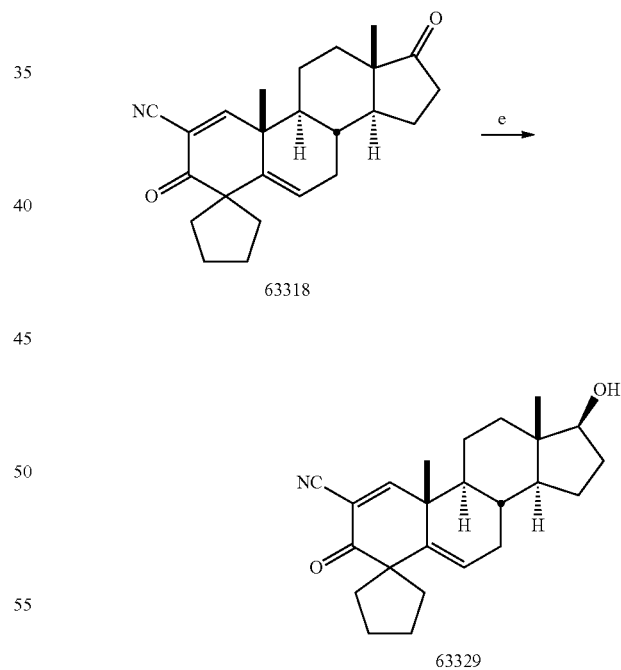
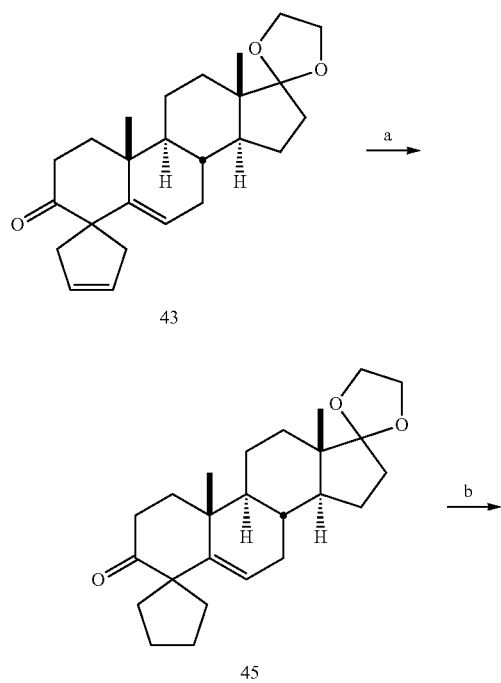
Scheme 11:





Reagents and conditions for Scheme 11: (a) Grubbs' catalyst (2nd generation), CH₂Cl₂, rt, 2 h, 99%; (b) LDA, THF, toluene, -78° C., 30 min; TsCN, -78° C., 30 min, 34%; (c) DDQ, benzene, 80° C., 30 min, 18%; (d) 1 N HCl (aq), THF, H₂O, rt, 14 h, 64%.

Scheme 12:

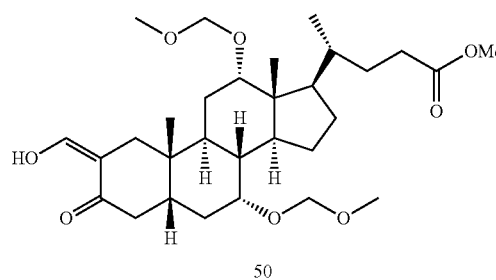
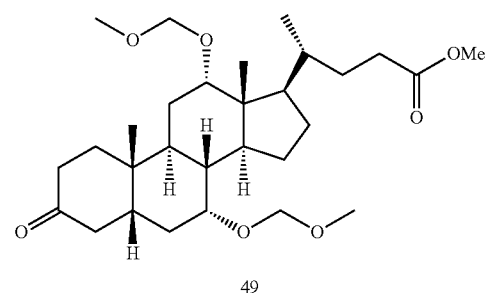
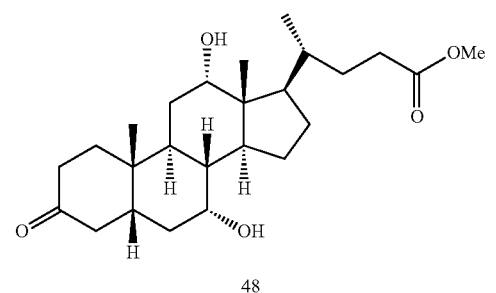
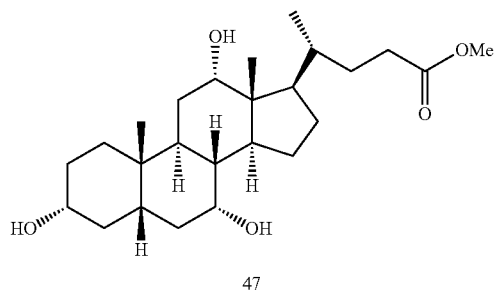
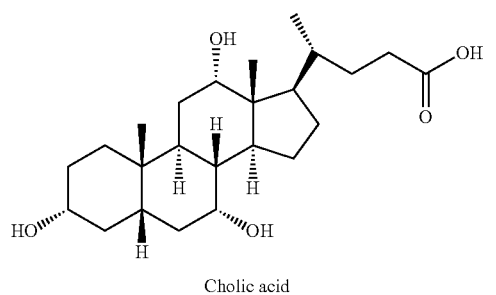


Reagents and conditions for Scheme 12: (a) H₂ (1 atm), 5% Pd/C, THF, 2 h, 98%; (b) LDA, THF, -78° C., 30 min; TsCN, -78° C., 30 min, 55%; (c) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0° C., 2 h; (ii) pyridine, 55° C., 21 h, 76% (d) 0.5 N HCl (aq), THF, rt, 50 h, 98%; (e) Al(Oi-Pr)₃, i-PrOH, toluene, 75° C., 20 h, 20%.

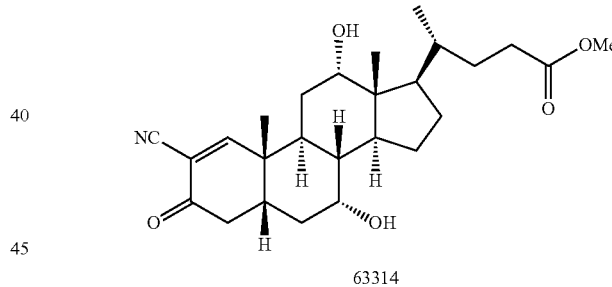
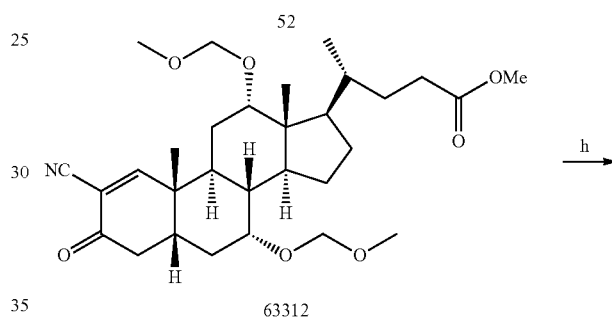
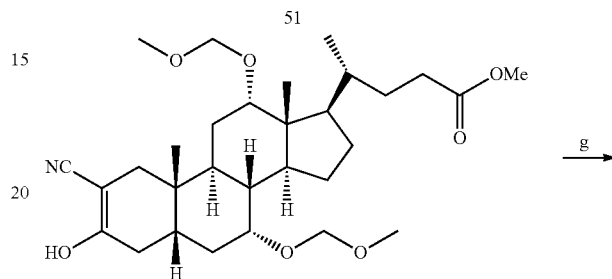
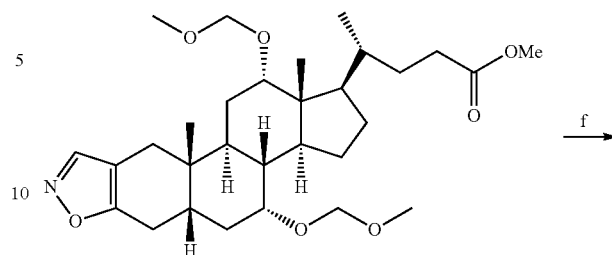
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Scheme 13a:



Scheme 13b:



Reagents and conditions for Schemes 13a and 13b: (a) AcCl, MeOH, rt, 72 h; (b) Ag₂CO₃/celite, toluene, reflux, 3 h, 66%; (c) MOM-Cl, i-Pr₂Net, CH₂Cl₂, 45° C., 14 h, 70%; (d) NaOMe, HCO₂Et, MeOH, rt, 2 h; (e) NH₂OH—HCl, EtOH, H₂O, 60° C., 14 h, 40%; (f) NaOMe, MeOH, THF, 55° C., 2 h, 41%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, rt, 3 h; (ii) pyridine, 55° C., 72 h, 80%; (h) 2 N HCl(Et₂O), CH₂Cl₂, rt, 14 h, 48%.

Example 3

Characterization of Certain Natural Products Including an Anti-Inflammatory Pharmacore

Compound 3:

A mixture of compound 1 (4.20 g, 24.4 mmol) and 2 (2.44 g, 24.4 mmol) in toluene (1 mL) was heated in a sealed vial at 130° C. for 16 h. After cooling to room temperature, THF (10 mL) and 0.1 N HCl (5 mL) were added. After stirring for 20

min, NaHCO₃ (aq) solution was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water, dried with MgSO₄ and concentrated. The residue obtained was purified by column chromatography (silica gel, 15% EtOAc in hexanes) to give compound 3 (2.84 g, 68%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 6.89 (d, 1H, J=10.4 Hz), 5.98 (d, 1H, J=10.4 Hz), 3.75 (s, 3H), 2.50 (m, 3H), 1.99 (m, 1H), 1.45 (s, 3H). The ¹H NMR spectrum is the same as reported in the literature (Danishefsky et al., 1979).

Compound 4:

LHMDS (1.0 M in THF, 3.75 mL, 3.75 mmol) was added dropwise to a solution of compound 3 (505 mg, 3.00 mmol) in THF (20 mL) at -78° C. After stirring for 1 h, MeI (0.56 mL, 9.00 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. After cooling to 0° C., NH₄Cl solution was added, and the mixture was extracted with CH₂Cl₂. The combined extracts were washed with water, dried with MgSO₄ and concentrated. The crude product obtained was dissolved in THF (20 mL) and cooled to -78° C. LHMDS (1.0 M in THF, 3.75 mL, 3.75 mmol) was added dropwise again. After stirring for 1 h at -78° C., MeI (0.56 mL, 9.00 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. After cooling to 0° C., NH₄Cl solution was added, and the mixture was extracted with CH₂Cl₂. The combined extracts were washed with water, dried with MgSO₄ and concentrated. The residue obtained was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give compound 4 (420 mg, 71%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 6.78 (dd, 1H, J=1.2, 10.2 Hz), 5.91 (d, 1H, J=10.2 Hz), 3.74 (s, 3H), 2.54 (dd, 1H, J=1.2, 14.1 Hz), 1.79 (d, 1H, J=14.1 Hz), 1.40 (s, 3H), 1.12 (s, 3H), 1.02 (s, 3H).

Compound 5:

A mixture of compound 4 (212 mg, 1.08 mmol), I₂ (824 mg, 3.24 mmol) and pyridine (1.5 mL) in CCl₄ (3 mL) was heated at 50° C. for 24 h. After cooling to room temperature, EtOAc (20 mL) was added. The mixture was washed with Na₂S₂O₃ solution, 1 N HCl (aq), and water, then dried with MgSO₄. After concentration, the residue obtained was purified by column chromatography (silica gel, 7% to 10% EtOAc in hexanes) to give compound 5 (313 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (s, 1H), 3.76 (s, 3H), 2.59 (d, 1H, J=14.4 Hz), 1.87 (d, 1H, J=14.4 Hz), 1.42 (s, 3H), 1.19 (s, 3H), 1.05 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 25.0, 26.0, 27.9, 41.4, 45.5, 46.9, 52.7, 103.0, 157.7, 174.6, 196.2.

Compound 6:

To a solution of compound 5 (200 mg, 0.62 mmol) in MeOH (6 mL) was added CeCl₃·7H₂O (255 mg, 0.68 mmol) and NaBH₄ (26 mg, 0.68 mmol) at 0° C. After stirring for 1 h, NaBH₄ (26 mg, 0.68 mmol) was added again and stirred for another 30 min. Water was added to the reaction mixture, and the mixture was extracted with EtOAc. The combined extracts were washed with water, dried with MgSO₄, and concentrated. The residue obtained was purified by column chromatography (silica gel, 10% to 20% EtOAc in hexanes) to give the allylic alcohol 6 (160 mg, 80%): ¹H NMR (400 MHz, CDCl₃) δ 6.51 (s, 1H), 3.77 (dd, 1H, J=1.2, 6.0 Hz), 3.69 (s, 3H), 2.34 (d, 1H, J=14.4 Hz), 2.00 (d, 1H, J=6.0 Hz), 1.42 (d, 1H, J=14.0 Hz), 1.26 (s, 3H), 1.07 (s, 3H), 0.84 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 19.1, 28.0, 28.6, 36.0, 44.5, 46.7, 52.3, 78.2, 107.3, 141.2, 175.8.

Compounds 8 and 9:

Imidazole (203 mg, 2.99 mmol) and TMSCl (190 μL, 1.49 mmol) was added successively to a solution of the alcohol 6 (160 mg, 0.50 mmol) in CH₂Cl₂ (3 mL) at 0° C. After stirring for 1 h, NaHCO₃ (aq) solution was added, and the mixture was extracted with CH₂Cl₂. The combined extracts were

dried with MgSO₄ and concentrated to give compound 7 (194 mg, 95%). Compound 7 was used in the next step without further purification.

DIBAL-H (1.0 M in toluene, 0.50 mL, 0.50 mmol) was added to compound 7 (194 mg, 0.47 mmol) in CH₂Cl₂ (5 mL) at -78° C. After stirring for 30 min, DIBAL-H (1.0 M in toluene, 0.50 mL, 0.50 mmol) was added again and stirred for another 30 min. K—Na tartrate (aq) solution was added, and the mixture was stirred at room temperature until clear. It was extracted with CH₂Cl₂, and the combined extracts were washed with water, dried with MgSO₄, and concentrated. The residue obtained was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give alcohol 8 (150 mg, 87%) and aldehyde 9 (11 mg, 6.4%). Compound 8: ¹H NMR (300 MHz, CDCl₃) δ 6.09 (s, 1H), 3.80 (s, 1H), 3.21 (m, 2H), 2.19 (t, 1H, J=5.4 Hz), 1.88 (d, 1H, J=14.4 Hz), 1.07 (d, 1H, J=14.4 Hz), 0.99 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H), 0.20 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 0.90, 24.8, 26.3, 27.7, 37.0, 37.6, 43.0, 71.2, 83.0, 100.5, 144.2.

NaHCO₃ (430 mg, 5.12 mmol) and Dess-Martin periodinane (434 mg, 1.02 mmol) in CH₂Cl₂ (2 mL) were stirred at room temperature for 20 min, and then a solution of alcohol 8 (150 mg, 0.41 mmol) in CH₂Cl₂ (20 mL) was added. After stirring for 2 h, Na₂S₂O₃ (aq) solution was added and stirred for 10 min. The mixture was extracted with hexanes, and the combined extracts were washed with NaHCO₃ (aq) solution, dried with MgSO₄, and concentrated. The residue obtained was purified by column chromatography (silica gel, 5% EtOAc in hexanes) to give aldehyde 9 (128 mg, 85%): ¹H NMR (300 MHz, CDCl₃) δ 9.37 (s, 1H), 6.29 (s, 1H), 3.89 (s, 1H), 2.11 (d, 1H, J=14.0 Hz), 1.29 (d, 1H, J=14.0 Hz), 1.10 (s, 3H), 1.01 (s, 3H), 0.83 (s, 3H), 0.23 (s, 9H).

Compound 12:

n-BuLi (2.5 M in hexanes, 1.46 mL, 3.65 mmol) was added to diisopropylamine (0.54 mL, 3.82 mmol) in THF (2 mL) at -78° C. After stirring at 0° C. for 30 min, it was cooled to -78° C. again. Compound 10 (500 mg, 3.47 mmol) in THF (5 mL) was then added dropwise. After stirring for 1 h, compound 11 (Cardona et al., 1986) (1.11 g, 4.17 mmol) was added and the resultant mixture was stirred at -78° C. for another 2 h. NH₄Cl (aq) was added to quench the reaction, and the mixture was extracted with ether. The combined extracts were washed with water and dried with MgSO₄. After concentration, the residue obtained was purified by column chromatography (silica gel, 10% to 20% EtOAc in hexanes) to give product 12 (1.0 g, 70%): ¹H NMR (400 MHz, CDCl₃) δ 6.73-6.89 (m, 3H), 5.10 (ddd, 1H, J=3.2, 6.4, 8.4 Hz), 3.81 (s, 3H), 3.72 (s, 3H), 3.20 (d, 1H, J=2.8 Hz), 2.88 (dd, 1H, J=8.8, 17.6 Hz), 2.80 (dd, 1H, J=3.6, 17.6 Hz), 1.37 (s, 3H), 1.35 (s, 3H), 0.99 (s, 9H), 0.14 (s, 6H).

Compound 13:

Et₃N (1.06 mL, 7.62 mmol) and MsCl (0.24 mL, 3.09 mmol) were added successively to a solution of compound 12 (1.00 g, 2.42 mmol) in CH₂Cl₂ (20 mL) at 0° C. After stirring for 30 min, NaHCO₃ (aq) solution was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water and dried with MgSO₄. After concentration, the residue obtained was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give product 13 (0.78 g, 81%): ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, 1H, J=16.0 Hz), 7.06 (m, 1H), 6.99 (bs, 1H), 6.83 (d, 1H, J=8.0 Hz), 6.63 (d, 1H, J=16.0 Hz), 3.84 (s, 3H), 3.71 (s, 3H), 1.43 (s, 6H), 0.98 (s, 9H), 0.16 (s, 6H).

Compound 14:

A mixture of compound 13 (3.70 g, 9.44 mmol), ethylene glycol (6.0 mL), and TsOH (0.80 g) in toluene (25 mL) was refluxed with a Dean-Stark apparatus for 4 h. After cooling to

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room temperature, the mixture was washed with NaHCO_3 (aq) solution and water, then dried over MgSO_4 . After concentration, the brown oil was dissolved in DMF (5 mL). Imidazole (2.70 g, 39.7 mmol) and TBSCl (1.50 g, 10 mmol) were added. After stirring for 30 min, TBSCl (500 mg, 3.33 mmol) was added again and stirred for an additional 30 min. NaHCO_3 (aq) solution was then added and the mixture was extracted with EtOAc. The combined extracts were washed with water and dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 10% to 15% EtOAc in hexanes) to give product 14 (1.71 g, 43%): ^1H NMR (400 MHz, CDCl_3) δ 6.85-6.90 (m, 2H), 6.79 (d, 1H, $J=8.4$ Hz), 6.60 (d, 1H, $J=16.0$ Hz), 6.07 (d, 1H, $J=16.0$ Hz), 3.95 (m, 4H), 3.83 (s, 3H), 3.70 (s, 3H), 1.30 (s, 6H), 1.00 (s, 9H), 0.15 (s, 6H).

Compound 15:

$n\text{-BuLi}$ (2.5 M in hexanes, 3.30 mL, 8.25 mmol) was added to dimethyl methylphosphonate (1.0 mL, 9.35 mmol) in THF (10 mL) at -78°C . After stirring for 15 min, a solution of compound 14 (1.20 g, 2.75 mmol) in THF (5 mL) was added dropwise. After stirring at room temperature for 2 h, NH_4Cl (aq) solution was added. The mixture was extracted with EtOAc and the combined extracts were washed with water and dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 50% to 100% EtOAc in hexanes) to give product 14 (1.32 g, 91%): ^1H NMR (400 MHz, CDCl_3) δ 6.84-6.89 (d, 2H), 6.79 (d, 1H, $J=8.0$ Hz), 5.57 (d, 1H, $J=16.0$ Hz), 5.87 (d, 1H, $J=16.0$ Hz), 3.90-4.01 (m, 4H), 3.82 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.47 (d, 2H, $J=20.4$ Hz), 1.26 (s, 6H), 0.99 (s, 9H), 0.15 (s, 6H).

Compound 16:

The condensation between compound 9 and 15 was performed using the procedure developed by Roush et al., 1984. MeCN (10 mL) and DIPEA (1.25 mL, 7.18 mmol) were added to a mixture of LiCl (121 mg, 2.85 mmol) and compound 15 (830 mg, 1.71 mmol) to give a yellow solution. Compound 9 (520 mg, 1.42 mmol) in MeCN (5 mL) was then added. The resultant reaction mixture was heated at 60°C for 20 h and cooled to room temperature. EtOAc was added and the mixture was washed with water, NaHCO_3 (aq) solution, and brine, then dried with MgSO_4 and concentrated. The residue obtained was purified by column chromatography (silica gel, 6% to 7% EtOAc in hexanes) to give product 16 (310 mg). The recovered starting materials 9 and 15 were treated again with the same reaction conditions to produce another 285 mg of product 16. The overall yield is 55%: ^1H NMR (400 MHz, CDCl_3) δ 6.82-6.86 (m, 2H), 6.77 (d, 1H, $J=8.0$ Hz), 6.70 (bs, 2H), 6.55 (d, 1H, $J=15.6$ Hz), 6.28 (s, 1H), 5.88 (d, 1H, $J=15.6$ Hz), 3.90 (m, 4H), 3.84 (bs, 1H), 3.81 (s, 3H), 1.80 (d, 1H, $J=14.8$ Hz), 1.40 (d, 1H, $J=14.8$ Hz), 1.22 (s, 6H), 1.11 (s, 3H), 0.99 (s, 3H), 0.98 (s, 9H), 0.83 (s, 3H), 0.23 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ -4.4, 1.4, 18.7, 20.7, 24.1, 25.9, 28.8, 28.9, 37.7, 42.9, 44.9, 54.1, 55.7, 64.9, 65.0, 81.5, 105.4, 110.3, 111.4, 120.4, 121.1, 124.1, 124.2, 130.1, 132.2, 143.3, 145.5, 151.2, 152.7, 201.7.

Compound 17:

$\text{Pd(PPh}_3)_4$ (90 mg, 0.078 mmol) in DMF (10 mL) was added to a mixture of compound 16 (595 mg, 0.77 mmol) and Zn(CN)_2 (363 mg, 3.10 mmol) at room temperature under Ar. The slurry was heated at 80°C for 20 min and cooled to room temperature. Ether was added, and the mixture was washed with water, dried with MgSO_4 and concentrated. The residue obtained was purified by column chromatography (silica gel, 5% to 10% EtOAc in hexanes) to give product 17 (352 mg, 68%): ^1H NMR (400 MHz, CDCl_3) δ 6.82-6.85 (m, 2H), 6.79 (d, 1H, $J=8.0$ Hz), 6.68 (m, 2H), 6.55 (d, 1H, $J=16.0$ Hz), 6.51

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(bs, 1H), 5.86 (d, 1H, $J=16.0$ Hz), 3.90 (m, 5H), 3.82 (s, 3H), 1.80 (d, 1H, $J=14.4$ Hz), 1.42 (d, 1H, $J=14.0$ Hz), 1.23 (s, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 0.99 (s, 9H), 0.95 (s, 3H), 0.78 (s, 3H), 0.23 (s, 9H), 0.15 (s, 6H).

Compound 18:

TsOH (240 mg, 1.26 mmol) was added to a solution of compound 17 (160 mg, 0.24 mmol) in acetone (5 mL) and water (1 mL) at room temperature. After stirring for 30 min, NaHCO_3 (aq) solution was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water and dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 20% to 33% EtOAc in hexanes) to give product 18 (142 mg, 99%): ^1H NMR (400 MHz, CDCl_3) δ 6.82-6.85 (m, 2H), 6.79 (d, 1H, $J=8.0$ Hz), 6.77 (d, 1H, $J=16.0$ Hz), 6.66 (d, 1H, $J=16.0$ Hz), 6.59 (m, 1H), 6.55 (d, 1H, $J=15.6$ Hz), 5.85 (d, 1H, $J=15.6$ Hz), 3.96 (dd, 1H, $J=1.6, 6.8$ Hz), 3.92 (m, 4H), 3.82 (s, 3H), 1.82 (d, 1H, $J=14.4$ Hz), 1.48 (d, 1H, $J=14.0$ Hz), 1.24 (s, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.99 (s, 9H), 0.80 (s, 3H), 0.15 (s, 6H). The compound was contaminated with some unidentified impurities.

Compound C0008:

Using the procedure described for the synthesis of compound 9 from compound 8, C0008 (110 mg, 77%) was produced from compound 18 (142 mg, 0.24 mmol): ^1H NMR (300 MHz, CDCl_3) δ 7.50 (d, 1H, $J=1.5$ Hz), 6.76-6.83 (m, 4H), 6.72 (d, 1H, $J=16.2$ Hz), 6.53 (d, 1H, $J=15.9$ Hz), 5.82 (d, 1H, $J=15.9$ Hz), 3.91 (m, 4H), 3.81 (s, 3H), 2.06 (dd, 1H, $J=1.5, 14.7$ Hz), 1.95 (d, 1H, $J=14.4$ Hz), 1.33 (s, 3H), 1.24 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.05 (s, 3H), 0.98 (s, 9H), 0.14 (s, 6H); m/z 616.3 ($\text{M}+\text{Na}^+$).

Compound C0009:

A mixture of C0008 (90 mg, 0.15 mmol), 6 N HCl (aq) (1 mL) and THF (5 mL) was stirred at room temperature overnight. EtOAc was added, and the mixture was washed with water, dried with MgSO_4 , and concentrated. The residue obtained was purified by column chromatography (silica gel, 33% EtOAc in hexanes) to give product C0009 (58 mg, 88%): ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, 1H, $J=15.3$ Hz), 7.39 (d, 1H, $J=1.5$ Hz), 7.10 (dd, 1H, $J=1.8, 8.4$ Hz), 6.89-6.98 (m, 3H), 6.56 (d, 1H, $J=15.3$ Hz), 6.12 (d, 1H, $J=15.3$ Hz), 5.93 (s, 1H), 3.94 (s, 3H), 2.03 (dd, 1H, $J=1.8, 14.7$ Hz), 1.92 (d, 1H, $J=14.4$ Hz), 1.42 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.11 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 20.8, 25.8, 25.9, 29.2, 39.4, 41.5, 47.0, 56.0, 60.4, 110.3, 114.0, 114.9, 115.7, 118.3, 123.4, 124.0, 126.4, 145.2, 146.8, 148.7, 151.1, 162.5, 196.2, 197.4, 197.6; m/z 458.1 ($\text{M}+\text{Na}^+$).

Compound C0010:

TBAF (1.0 M in THF, 74 μL , 0.074 mmol) was added to a solution of C0008 (40 mg, 0.067 mmol) in THF (3 mL). After stirring for 10 min, EtOAc was added. The mixture was washed with water, dried with MgSO_4 , and concentrated. The residue obtained was purified by column chromatography (silica gel, 33% EtOAc in hexanes) to give product C0010 (20 mg, 63%): ^1H NMR (400 MHz, CDCl_3) δ 7.49 (d, 1H, $J=1.6$ Hz), 6.86 (m, 3H), 6.84 (d, 1H, $J=16.0$ Hz), 6.72 (d, 1H, $J=16.0$ Hz), 6.53 (d, 1H, $J=16.0$ Hz), 5.82 (d, 1H, $J=16.0$ Hz), 5.71 (s, 1H), 3.92 (bs, 7H), 2.06 (dd, 1H, $J=2.0, 14.4$ Hz), 1.95 (d, 1H, $J=14.4$ Hz), 1.34 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 1.06 (s, 3H); m/z 480.2 ($\text{M}+1$).

Compound 20:

A mixture of K_2CO_3 (7.00 g, 50.7 mmol) and compound 19 (2.70 g, 9.44 mmol) in MeOH (150 mL) was stirred at room temperature for 2 h. The mixture was filtered, and the filtrate obtained was concentrated to give the crude potassium salt, which was suspended in THF (50 mL). DIPEA (5.42 mL, 31.2 mmol) and MOMCl (2.70 mL, 35.5 mmol) were added

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successively. The white slurry was stirred at room temperature overnight. EtOAc was added, and the mixture was washed with water, dried with MgSO_4 , and concentrated. The oil obtained was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give product 20 (2.53 g, 94%).

Compound 21:

A mixture of compound 3 (280 mg, 1.67 mmol), I_2 (630 mg, 2.48 mmol), and pyridine (2 mL) in CCl_4 (4 mL) was stirred at room temperature for 16 h. EtOAc was added, and the mixture was washed with $\text{Na}_2\text{S}_2\text{O}_3$ (aq) solution, 1 N HCl (aq), and water, then dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 12% EtOAc in hexanes) to give compound 21 (364 mg, 74%): ^1H NMR (300 MHz, CDCl_3) δ 7.68 (s, 1H), 3.77 (s, 3H), 2.69-2.74 (m, 2H), 2.52 (m, 1H), 2.04 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.7, 32.5, 33.4, 48.0, 52.8, 104.3, 159.6, 173.3, 191.1.

Compound 22:

A mixture of compound 21 (370 mg, 1.26 mmol), ethylene glycol (1 mL), PPTS (80 mg) in toluene (3 mL) was heated at reflux with a Dean-Stark apparatus for 3 h. After cooling to room temperature, EtOAc was added. The mixture was washed with NaHCO_3 (aq) solution, water, and dried with MgSO_4 . After concentration, crude product 22 (400 mg, 94%) was obtained, which was used in the next step without further purification. Compound 22: ^1H NMR (300 MHz, CDCl_3) δ 6.65 (s, 1H), 4.21 (m, 2H), 3.98 (m, 2H), 3.69 (s, 3H), 2.30 (m, 1H), 1.96 (m, 2H), 1.75 (m, 1H), 1.30 (s, 3H).

Compounds 23, 24:

Using the procedure described for the synthesis of compounds 8 and 9 from compound 7, compound 23 (185 mg, 50%) and 24 (150 mg, 41%) was produced from compound 22 (400 mg, 1.18 mmol).

Using the procedure described for the synthesis of compound 9 from compound 8, compound 24 (158 mg, 85%) was produced from compound 23 (185 mg, 0.60 mmol).

Compound 23:

^1H NMR (400 MHz, CDCl_3) δ 6.45 (s, 1H), 4.21 (m, 2H), 3.98 (m, 2H), 3.39 (m, 2H), 1.85-2.00 (m, 4H), 1.54 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.2, 28.7, 30.5, 42.4, 65.4, 65.6, 69.7, 104.5, 105.8, 149.6.

Compound 24:

^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 6.47 (s, 1H), 4.21 (m, 2H), 3.98 (m, 2H), 2.16 (m, 1H), 1.94 (m, 2H), 1.71 (m, 1H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 27.3, 30.6, 52.1, 65.7, 65.8, 105.1, 107.4, 143.4, 199.9.

Compound 25:

Potassium t-butoxide (790 mg, 7.05 mmol) in THF (20 mL) was added to a solution of compound 20 (2.13 g, 7.39 mmol) in THF (10 mL) at 0°C . After stirring for 45 min, a solution of compound 24 (512 mg, 1.67 mmol) in THF (10 mL) was added. The mixture was stirred at 0°C for 1 h and at room temperature for another 1 h. EtOAc was added, and the mixture was washed with water and dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 12% EtOAc in hexanes) to give product 25 (680 mg, 89%): ^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, 2H, $J=10.4$ Hz), 6.97 (d, 2H, $J=10.4$ Hz), 6.47 (s, 1H), 6.27 (d, 1H, $J=16.4$ Hz), 5.92 (d, 1H, $J=16.0$ Hz), 5.16 (s, 2H), 4.22 (m, 2H), 3.97 (m, 2H), 3.48 (s, 3H), 1.94 (m, 2H), 1.80 (m, 2H), 1.12 (s, 3H); NMR (100 MHz, CDCl_3) δ 27.2, 30.6, 33.3, 43.0, 55.9, 65.4, 65.8, 94.3, 103.4, 105.9, 116.2, 127.3, 128.0, 130.9, 133.7, 150.4, 156.6.

Compound 26:

Using the procedure described for the synthesis of compound 17 from compound 16, compound 26 (36 mg, 62%) was produced from compound 25 (75 mg, 0.17 mmol). ^1H

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NMR (400 MHz, CDCl_3) δ 7.28 (d, 2H, $J=10.4$ Hz), 6.98 (d, 2H, $J=10.4$ Hz), 6.54 (s, 1H), 6.21 (d, 1H, $J=16.4$ Hz), 5.91 (d, 1H, $J=16.0$ Hz), 5.17 (s, 2H), 4.24 (m, 2H), 3.96-4.07 (m, 2H), 3.47 (s, 3H), 1.78-1.89 (m, 4H), 1.27 (s, 3H).

Compound R00141:

TsOH (77 mg, 0.40 mmol) was added to a solution of compound 26 (36 mg, 0.081 mmol) in acetone (3 mL) at room temperature, and acetone was removed under reduced pressure to give a white solid, which was dried under vacuum (2 mm Hg) for 2 min. Acetone (10 mL) and NaHCO_3 (1.0 g) were added. After stirring for 5 min, the mixture was filtered through a pad of celite. The filtrate was concentrated and the crude product was purified by column chromatography (silica gel, 15% to 25% EtOAc in hexanes) to give product R00141 (18 mg, 87%): ^1H NMR (400 MHz, CDCl_3) δ 7.47 (d, 1H, $J=1.2$ Hz), 7.25 (d, 2H, $J=9.2$ Hz), 6.82 (d, 2H, $J=8.8$ Hz), 6.27 (d, 1H, $J=16.4$ Hz), 5.96 (d, 1H, $J=16.4$ Hz), 5.26 (bs, 1H), 2.52-2.66 (m, 2H), 2.04-2.14 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.8, 33.6, 34.2, 40.0, 114.0, 115.7, 116.4, 127.8, 128.6, 129.2, 130.5, 155.8, 167.6, 192.1.

Compound 27:

TsOH (5.04 g, 26.5 mmol) was added to a solution of compound 25 (680 mg, 1.50 mmol) in acetone (25 mL) and water (5 mL). The mixture was stirred at room temperature until compound 25 was completely consumed by TLC analysis. EtOAc was added, and the mixture was washed with water, NaHCO_3 (aq) solution, and dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give product 27 (550 mg, 89%): ^1H NMR (300 MHz, CDCl_3) δ 7.52 (s, 1H), 7.28 (m, 2H), 7.00 (m, 2H), 6.33 (d, 1H, $J=16.2$ Hz), 5.98 (d, 1H, $J=16.2$ Hz), 5.18 (s, 2H), 3.48 (s, 3H), 2.68 (m, 2H), 2.09 (m, 2H), 1.37 (s, 3H).

Compound 28:

Using the procedure described for the synthesis of compound 4 from compound 3, compound 28 (280 mg, 48%) was produced from compound 27 (550 mg, 1.34 mmol). From this reaction, a mixture of compound 28 and 29 (85 mg, 14%) was also obtained.

Compound 28:

^1H NMR (400 MHz, CDCl_3) δ 7.61 (s, 1H), 7.28 (d, 2H, $J=8.8$ Hz), 6.99 (d, 2H, $J=8.8$ Hz), 6.29 (d, 1H, $J=16.4$ Hz), 6.07 (d, 1H, $J=16.4$ Hz), 5.17 (s, 2H), 3.47 (s, 3H), 2.05 (dd, 1H, $J=1.2$, 14.4 Hz), 1.99 (d, 1H, $J=14.0$ Hz), 1.32 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 27.1, 27.8, 29.9, 42.0, 43.2, 48.6, 55.9, 94.3, 102.8, 116.3, 127.2, 128.0, 130.5, 134.8, 156.8, 162.6, 197.2.

Compound 30:

Using the procedure described for the synthesis of compound 17 from compound 16, compound 30 (90 mg, 42%) was produced from compound 28 (280 mg, 0.66 mmol): ^1H NMR (400 MHz, CDCl_3) δ 7.56 (d, 1H, $J=1.6$ Hz), 7.28 (m, 2H), 7.01 (m, 2H), 6.26 (d, 1H, $J=16.4$ Hz), 6.07 (d, 1H, $J=16.4$ Hz), 5.18 (s, 2H), 3.47 (s, 3H), 2.07 (dd, 1H, $J=1.6$, 14.8 Hz), 1.96 (d, 1H, $J=14.8$ Hz), 1.39 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.3, 26.5, 29.7, 39.4, 41.7, 47.8, 56.0, 94.2, 114.5, 114.9, 116.4, 127.3, 128.9, 130.0, 133.3, 157.1, 165.7, 197.2.

Compound C00142:

Using the procedure described for the synthesis of C00141 from compound 26, compound C00142 (70 mg, 93%) was produced from compound 30 (90 mg, 0.27 mmol): ^1H NMR (300 MHz, CDCl_3) δ 7.56 (d, 1H, $J=1.5$ Hz), 7.21 (m, 2H), 6.83 (m, 2H), 6.23 (d, 1H, $J=16.5$ Hz), 6.07 (bs, 1H), 6.01 (d, 1H, $J=16.5$ Hz), 2.04 (dd, 1H, $J=1.5$, 14.7 Hz), 1.94 (d, 1H, $J=14.7$ Hz), 1.37 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H); ^{13}C NMR

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(75 MHz, CDCl_3) δ 26.3, 26.5, 29.6, 39.4, 41.7, 47.7, 114.5, 114.7, 115.7, 127.5, 128.7, 129.1, 132.5, 155.9, 166.4, 197.7; m/e 282.1 (M+1).

R00142-1:

Using the procedure described for the synthesis of C00142 from compound 28, C00142-1 (a 1:1 mixture of 31 and C00142) was prepared from a mixture of compound 28 and 29 (2 mg, 4.6 μmol). The ^1H NMR that can be identified for compound 31 is: (400 MHz, CDCl_3) δ 7.41 (d, 1H, $J=2.4$ Hz), 6.23 (d, 1H, $J=16.4$ Hz), 5.97 (d, 1H, $J=16.4$ Hz), 2.61 (m, 1H), 1.39 (s, 3H), 1.15 (d, 3H, $J=6.8$ Hz); LC-MS shows the retention time for compound 31 and C00142 are 6.52 min with m/z 290.0 (M+Na $^+$) and 7.36 min with m/z 304.0 (M+Na $^+$) respectively.

Compound 32:

Testosterone (5.19 g, 18.0 mmol) was added in one portion to a solution of t-BuOK (5.96 g, 53.2 mmol) in t-BuOH (100 mL) at room temperature. After stirring for 5 min, MeI (6.64 mL, 106.4 mmol) was added dropwise over 10 min. After stirring at room temperature for 4 h, water (75 mL) was added, and t-BuOH was removed under reduced pressure. The white solid that precipitated was collected by filtration and washed with water. The white solid was dissolved in CH_2Cl_2 , dried with MgSO_4 and concentrated. The crude product was recrystallized from acetone (80 mL) to give compound 32 (3.50 g, 62%) as a white crystalline solid: ^1H NMR (400 MHz, CDCl_3) δ 5.56 (dd, 1H, $J=2.8, 6.8$ Hz), 3.66 (m, 1H), 2.40-2.62 (m, 2H), 1.99-2.19 (m, 3H), 1.86 (m, 1H), 1.26-1.70 (m, 9H), 1.24 (s, 6H), 0.94-1.18 (m, 3H), 0.87 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.0, 19.3, 20.8, 23.3, 27.2, 30.2, 30.5, 31.2, 31.2, 32.0, 33.6, 36.5, 37.1, 42.7, 48.6, 49.0, 51.3, 81.7, 119.6, 149.8, 216.7.

Compound 33:

Compound 32 (1.05 g, 3.32 mmol) and 10% Pd on carbon (500 mg) in EtOH (50 mL) was hydrogenated (1 atm) for 16 h at room temperature. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated to give crude product, which was purified by column chromatography (silica gel, 5% to 9% CH_2Cl_2 in EtOAc) to give compound 33 (400 mg, 38%) as white solid: ^1H NMR (300 MHz, CDCl_3) δ 3.63 (m, 1H), 2.63 (ddd, 1H, $J=6.6, 12.9, 15.5$ Hz), 2.32 (ddd, 1H, $J=3.3, 5.4, 15.5$ Hz), 1.92-2.14 (m, 2H), 1.77-1.83 (m, 2H), 1.19-1.65 (m, 11H), 1.08 (m, 1H), 1.06 (s, 6H), 1.05 (s, 3H), 0.65-0.95 (m, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.1, 14.0, 20.4, 21.8, 22.3, 23.3, 25.7, 30.5, 32.0, 34.6, 35.2, 36.5, 36.5, 38.1, 42.9, 47.8, 50.9, 55.5, 55.8, 81.8, 217.4.

Compound 34:

Imidazole (125 mg, 1.84 mmol) and TMSCl (155 μL , 1.22 mmol) were added to a solution of compound 33 (195 mg, 0.61 mmol) in CH_2Cl_2 (6.0 mL) at room temperature. After stirring for 1 h, the reaction mixture was washed with NaHCO_3 (aq) solution, dried with MgSO_4 and concentrated. The residue obtained was purified by column chromatography (silica gel, 5% hexanes in ether) to give compound 34 (200 mg, 84%): ^1H NMR (400 MHz, CDCl_3) δ 3.53 (dd, 1H, $J=8.0, 8.4$ Hz), 2.63 (ddd, 1H, $J=7.2, 13.2, 15.2$ Hz), 2.32 (ddd, 1H, $J=3.2, 5.2, 15.2$ Hz), 1.97 (ddd, 1H, $J=3.2, 5.6, 13.2$ Hz), 1.71-1.91 (m, 3H), 1.19-1.59 (m, 10H), 1.06 (s, 3H), 1.05 (s, 6H), 0.78-0.99 (m, 3H), 0.70 (s, 3H), 0.66 (m, 1H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 0.1, 11.3, 13.9, 20.5, 21.7, 22.3, 23.4, 25.7, 30.8, 32.1, 34.7, 35.2, 36.5, 36.8, 38.1, 42.9, 47.8, 50.6, 55.6, 56.0, 81.6, 217.3.

Compound D0016:

n-BuLi (2.5 M in hexanes, 0.41 mL, 1.03 mmol) was added to diisopropylamine (159 μL , 1.12 mmol) in THF (0.6 mL) at -78°C . After stirring at 0°C . for 30 min, the reaction mixture

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was cooled to -78°C . again, and compound 34 (200 mg, 0.51 mmol) in THF (2 mL) was added dropwise. After stirring for 30 min at -78°C ., TsCN (371 mg, 2.04 mmol) in THF (2.0 mL) was added. After stirring for another 30 min, water (1 mL) was added to quench the reaction. The reaction mixture was adjusted to pH 3 using 3 N HCl (aq) and extracted with EtOAc. The combined extracts were washed with water, dried with MgSO_4 and concentrated. The crude product obtained was dissolved in benzene (15 mL) and DDQ (116 mg, 0.51 mmol) was added. The red solution was refluxed for 20 min and cooled to room temperature. The reaction mixture was washed with NaHCO_3 (aq) solution and water, then dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 0 to 5% EtOAc in CH_2Cl_2) to give D0016 (106 mg, 50%): ^1H NMR (400 MHz, CDCl_3) δ 7.84 (s, 1H), 3.55 (dd, 1H, $J=8.4, 8.4$ Hz), 1.80-1.92 (m, 3H), 1.64-1.73 (m, 3H), 1.40-1.58 (m, 5H), 1.26 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H), 0.86-1.16 (m, 4H), 0.73 (s, 3H), 0.08 (s, 9H).

Compound D0017:

p-TsOH (220 mg, 1.16 mmol) was added to a solution of D0016 (95 mg, 0.23 mmol) in acetone (2 mL) and water (0.4 mL). After stirring at room temperature for 5 min, NaHCO_3 (aq) solution was added, and the mixture was extracted with CH_2Cl_2 . The combined extracts were dried with MgSO_4 and concentrated. The crude product obtained was purified by column chromatography (silica gel, 33% EtOAc in hexanes) to give D0017 (75 mg, 95%): ^1H NMR (300 MHz, CDCl_3) δ 7.85 (s, 1H), 3.67 (dd, 1H, $J=8.4, 8.7$ Hz), 2.08 (m, 1H), 1.20-1.96 (m, 12H), 1.19 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H), 0.86-1.14 (m, 4H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.5, 16.1, 20.7, 21.6, 22.0, 23.5, 27.0, 30.6, 31.5, 35.6, 36.5, 40.8, 43.2, 45.1, 51.1, 51.3, 51.9, 81.6, 114.7, 115.3, 168.8, 198.2.

Compound D0018:

NaHCO_3 (140 mg, 1.66 mmol) and Dess-Martin periodinane (177 mg, 0.42 mmol) were added successively to a solution of D0017 (57 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) at room temperature. After stirring for 2 h, 5% $\text{Na}_2\text{S}_2\text{O}_3$ (aq) solution was added. The reaction mixture was extracted with ether, and the combined extracts were washed with NaHCO_3 (aq) solution, dried with MgSO_4 and concentrated. The crude product obtained was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to give D0018 (45 mg, 79%) which was contaminated with some impurities. Recrystallization from EtOAc/hexanes afforded purified D0018 (38 mg) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.84 (s, 3H), 2.48 (m, 1H), 1.26-2.18 (m, 12H), 1.21 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.08 (m, 1H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.8, 15.8, 20.1, 21.2, 21.6, 21.7, 26.7, 30.5, 31.0, 34.8, 35.6, 40.5, 44.8, 47.5, 50.9, 51.1, 51.5, 114.6, 114.8, 167.8, 197.7, 219.9.

Compound 35:

Diisopropylethylamine (12.2 mL, 70.0 mmol), MOMCl (2.66 mL, 35.0 mmol) and DMAP (0.21 g, 1.7 mmol) were added successively to a stirred solution of testosterone (5.05 g, 17.5 mmol) in CH_2Cl_2 (50 mL). After stirring at room temperature for 14 h, NaHCO_3 (aq) solution was added. After stirring for 10 min, the organic layer was separated, washed with 1 N HCl (aq), NaHCO_3 (aq) solution, and water, then dried with MgSO_4 . After concentration, the residue obtained was purified by column chromatography (silica gel, 9% to 33% EtOAc in hexanes) to give compound 35 (5.66 g, 98%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 5.73 (bs, 1H), 4.63 (m, 2H), 3.53 (dd, 1H, $J=8.4, 8.4$ Hz), 3.35 (s, 3H), 2.32-2.47 (m, 3H), 2.28 (m, 1H), 2.04 (m, 2H), 1.90 (m, 1H),

1.85 (m, 1H), 1.24-1.75 (m, 7H), 1.19 (s, 3H), 1.15 (m, 1H), 0.88-1.06 (m, 3H), 0.82 (s, 3H).

Compounds D0014 and D0015:

A solution of compound 35 (1.66 g, 5.0 mmol) in MeOH (80 mL) was treated with 30% H₂O₂ (aq) (3.52 mL, 35.2 mmol) and NaOH (aq) solution (2.5 N, 1.40 mL, 3.50 mmol) at 0° C. After stirring at 4° C. for 14 h, water (200 mL) was added, and the reaction mixture was extracted with EtOAc. The combined organic layer was washed with water, dried with MgSO₄ and concentrated to give epoxide 36 (1.24 g, 71%) as mixture of epimers. A solution of epoxide 36 (1.20 g, 3.47 mmol) in EtOH (60 mL) was treated with a solution of NaCN (1.70 g, 34.7 mmol) in water (18 mL). After refluxing for 24 h, EtOH was removed by evaporation. 10% NaOH (aq) solution (30 mL) was added at room temperature, and the mixture was extracted with ether. The aqueous layer was acidified with 6 N HCl (aq) (30 mL) at 0° C. to pH 2 and extracted with EtOAc. The combined EtOAc extracts were washed with water, dried with MgSO₄ and concentrated to give crude 37 as a white foam solid. Compound 37 was heated at 210° C. under vacuum (5 mmHg) for 40 min and cooled to room temperature. The brown viscous oil was purified by column chromatography (silica gel, 33% to 50% EtOAc in hexanes) to give compound D0014 (290 mg, 23% from 36) and D0015 (260 mg, 23% from 36) as white solids.

D0014:

¹H NMR (400 MHz, CDCl₃) δ 4.63 (m, 2H), 3.54 (dd, 1H, J=8.4 Hz), 3.35 (s, 3H), 3.07 (ddd, 1H, J=2.4, 3.6, 15.2 Hz), 1.90-2.13 (m, 4H), 1.43-1.80 (m, 7H), 1.30-1.40 (m, 2H), 1.27 (s, 3H), 1.10-1.21 (m, 2H), 0.94-1.10 (m, 2H), 0.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 11.6, 18.0, 20.5, 23.1, 27.9, 31.1, 32.0, 33.0, 34.0, 34.9, 36.6, 40.2, 42.4, 50.1, 53.7, 55.1, 86.0, 95.9, 112.1, 114.0, 184.0, 192.3; m/z 358.2 (M+1).

D0015:

¹H NMR (300 MHz, CDCl₃) δ 3.67 (dd, 1H, J=8.4 Hz), 3.07 (ddd, 1H, J=2.7, 3.9, 15.3 Hz), 2.40-2.56 (m, 3H), 1.96-2.16 (m, 3H), 1.89 (ddd, 1H, J=3.0, 3.6, 12.6 Hz), 1.57-1.79 (m, 5H), 1.43-1.55 (m, 2H), 1.34 (m, 1H), 1.28 (s, 3H), 0.80-1.20 (m, 4H), 0.80 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 11.0, 18.0, 20.6, 23.2, 30.3, 31.2, 32.0, 33.0, 34.0, 35.1, 36.1, 40.3, 42.7, 50.1, 53.7, 81.3, 112.1, 114.0, 184.1, 192.4; m/z 314.1 (M+1).

Compound 39:

A mixture of compound 38 (Barton et al., 1980) (350 mg, 0.74 mmol) and K₂CO₃ (514 mg, 3.72 mmol) in MeOH (5 mL) was stirred at room temperature for 4 h. Ether was added, and the mixture was washed with water. The combined aqueous phases were extracted with CH₂Cl₂. The combined organic extracts were dried with MgSO₄ and concentrated. The residue obtained was dissolved in CH₂Cl₂ (10 mL). NaOAc (183 mg, 2.23 mmol) and PCC (322 mg, 1.49 mmol) were added at room temperature. After stirring for 2 h, additional PCC (160 mg, 0.74 mmol) was added and stirred for another 1 h. A mixture of hexanes/EtOAc (1:1, 20 mL) was added and stirred for 5 min. The brown slurry was filtered through a pad of silica gel, and the filtrate was concentrated. The residue obtained was purified by column chromatography (silica gel, 25% to 33% EtOAc in hexanes) to give compound 39 (300 mg, 95%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.73 (d, 1H, J=1.6 Hz), 4.39 (m, 1H), 3.49 (ddd, 1H, J=2.0, 4.0, 10.8 Hz), 3.34 (dd, 1H, J=10.8, 10.8 Hz), 2.17-2.60 (m, 7H), 2.04-2.10 (m, 2H), 1.40-1.85 (m, 12H), 1.27 (s, 3H), 1.14 (m, 1H), 1.10 (d, 3H, J=7.2 Hz), 0.94 (s, 3H), 0.79 (d, 3H, J=6.8 Hz); m/z 427.2 (M+1).

Compound H0001:

Freshly prepared LDA solution (1.0 M, 0.18 mL, 0.18 mmol) was added dropwise to a solution of compound 39 (50

mg, 0.12 mmol) in THF (1 mL) at -78° C. After stirring for 45 min, TsCN (43 mg, 0.24 mmol) in THF (0.5 mL) was added. After stirring for another 30 min, NH₄Cl (aq) solution was added to quench the reaction. The reaction mixture was adjusted to pH 3 using 3 N HCl (aq) and extracted with EtOAc. The combined EtOAc extracts were washed with water, dried with MgSO₄, and concentrated. The crude product obtained was dissolved in benzene (1 mL), and DDQ (25 mg, 0.13 mmol) was added. The red solution was refluxed for 20 min and then cooled to room temperature. The reaction mixture was washed with NaHCO₃ (aq) solution and water, then dried with MgSO₄ and concentrated. The residue obtained was purified by column chromatography (silica gel, 33% EtOAc in hexanes) to give H0001 (19 mg, 37%): ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 5.84 (d, 1H, J=2.0 Hz), 4.41 (m, 1H), 3.50 (ddd, 1H, J=2.4, 4.0, 11.2 Hz), 3.35 (d, 1H, J=10.8, 11.2 Hz), 2.61 (m, 1H), 2.48-2.52 (m, 2H), 2.42 (dd, 1H, J=7.2, 8.8 Hz), 2.13-2.27 (m, 3H), 1.51-1.88 (m, 9H), 1.44 (m, 1H), 1.39 (s, 3H), 1.20 (m, 1H), 1.11 (d, 3H, J=7.2 Hz), 0.97 (s, 3H), 0.80 (d, 3H, J=6.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.1, 15.0, 17.1, 19.0, 26.3, 28.7, 30.1, 31.3, 31.3, 31.7, 36.4, 39.5, 40.9, 42.5, 43.1, 50.9, 52.2, 53.6, 66.9, 79.4, 109.4, 113.7, 116.4, 120.6, 162.1, 164.1, 190.6, 203.0; m/z 450.2 (M+1).

Compound 40:

To a mixture of ethylene glycol (6.4 g, 104 mmol) and camphorsulfonic acid (40 mg, 0.17 mmol) in cyclohexane (25 mL) was added dehydroepiandrosterone (5.0 g, 17.3 mmol). The suspension was heated at reflux with a Dean-Stark trap for 20 h. After cooling, the mixture was diluted with sat. sodium bicarbonate (50 mL) and extracted with EtOAc (2×100 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give compound 40 (5.7 g, 99%) as a white solid: m/z 333.1 (M+1).

Compound 41:

To a solution of compound 40 (2.60 g, 7.82 mmol) in toluene (50 mL) was added 3-methyl-2-butanone (25 mL) followed by aluminum tri-isopropoxide (2.4 g, 11.73 mmol). The mixture was heated at reflux for 4 h. After cooling, the mixture was diluted with MTBE (100 mL) and washed with sat. potassium dihydrogen phosphate (50 mL). The aqueous layer was extracted with MTBE (2×50 mL). The combined organic extracts were washed with water, brine, dried over MgSO₄, concentrated, and dried under vacuum to give crude yellow solid. The crude product was purified by column chromatography (10% EtOAc/CH₂Cl₂) to give product 41 (1.87 g, 72%) as a white solid: m/z 331.0 (M+1).

Compound 42:

To a solution of potassium t-butoxide in THF (57.5 mL of 1 M solution, 57.5 mmol) was added t-butanol (28 mL). Compound 41 (3.80 g, 11.50 mmol) was added, and the resulting solution was stirred for 30 minutes. Allyl bromide (2.78 g, 23.0 mmol) was added, and the mixture was stirred for 2 h. Sat. NH₄Cl (aq) (50 mL) was added, and the mixture was diluted with water (50 mL) and extracted with MTBE (2×100 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give crude product. The crude product was purified by column chromatography (10-20% EtOAc/hexane) to give product 42 (3.46 g, 73%) as a white solid: m/z 411.1 (M+1).

Compound 43:

To a solution of diisopropylamine (0.54 mL, 3.81 mmol) in THF (5 mL) at -78° C. was added n-BuLi (2.21 mL of a 1.6 M solution in hexane, 3.53 mmol). The solution was allowed to warm to 0° C. and stirred for 20 min, then re-cooled to -78° C. A solution of compound 42 (0.58 g, 1.41 mmol) in THF (2

mL) was added dropwise, and the solution was stirred 30 min. A solution of tosyl cyanide (0.28 g, 1.55 mmol) in THF (2 mL) was added dropwise, and the solution was stirred 30 min. Water (5 mL) was added, and the mixture was allowed to warm to room temperature. The aqueous phase was adjusted to pH 4 with 1 N HCl (aq) and extracted with MTBE (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give crude product. The crude product was purified by column chromatography (25% EtOAc/hexane) to give compound 43 (0.35 g, 57%) as a white foam solid: m/z 436.1 (M+1).

Compound 44:

A solution of compound 43 (0.34 g, 0.78 mmol) in THF (10 mL) was placed under N₂ atmosphere. 10% Pd/C (25 mg) was added, and the mixture was evacuated and purged with H₂ (3×). The mixture was stirred under a H₂ balloon for 2 h, then filtered through a fine fitted filter. The filtrate was concentrated to give compound 44 (0.34 g, 100%) as a white foam solid: m/z 440.2 (M+1).

Compound 63313:

To a solution of compound 44 (0.34 g, 0.77 mmol) in benzene (8 mL) was added DDQ (176 mg, 0.77 mmol), and the solution was heated at 80° C. for 3 h. After cooling, the mixture was diluted with EtOAc (50 mL), washed with sat. NaHCO₃ (aq), brine, dried over MgSO₄, and concentrated to give crude product as a dark foam. The crude product was purified by column chromatography (15-25% EtOAc/hexane) to give impure product 63313 (95 mg) as an off-white foam solid, which was taken up in THF (4 mL) and 1M HCl (1 mL) and stirred 2 h. The mixture was diluted with sat. NaHCO₃ (aq), and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give crude product. The crude product was purified by column chromatography (15% EtOAc/hexane) to give compound 63313 (34 mg, 10%) as a white foam solid: ¹H NMR (500 MHz, CDCl₃) δ 7.67 (s, 1H), 5.59 (br s, 1H), 2.53 (dd, J=19 and 9 Hz, 1H), 2.44 (br d, J=19 Hz, 1H), 2.20-2.08 (m, 1H), 2.05-1.35 (m, 14H), 1.30 (s, 3H), 1.30-1.08 (m, 3H), 1.05-0.90 (m, 1H), 0.96 (s, 3H), 0.89 (t, J=7 Hz, 3H), 0.85 (t, J=7 Hz, 3H); m/z 394.1 (M+1).

Compound 43:

To a solution of compound 42 (0.87 g, 2.12 mmol) in CH₂Cl₂ (100 mL) was added the 2nd generation Grubbs catalyst (90 mg, 0.11 mmol), and the solution was stirred at room temperature for 2 h. Most of the CH₂Cl₂ was removed via rotary evaporation. The crude product was purified by column chromatography (15% EtOAc/hexane) to give compound 43 (0.80 g, 99%) as a white crystalline solid: m/z 383.0 (M+1).

Compound 44:

To a solution of di-isopropylamine (0.39 mL, 2.73 mmol) in THF (5 mL) at -78° C. was added n-BuLi (1.58 mL of a 1.6 M solution in hexane, 2.53 mmol). The solution was allowed to warm to 0° C. and stirred for 20 min, then re-cooled to -78° C. A solution of compound 43 (0.387 g, 1.01 mmol) in THF (15 mL) and toluene (10 mL) was added dropwise, and the solution was stirred 30 min. A solution of tosyl cyanide (0.22 g, 1.21 mmol) in THF (3 mL) was added dropwise, and the solution was stirred 30 min. Water (5 mL) was added, and the mixture was allowed to warm to room temperature. The aqueous phase was adjusted to pH 4 with 1 N HCl (aq) and extracted with MTBE (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum. The crude product was purified

by column chromatography (20% EtOAc/hexane) to give compound 44 (0.14 g, 34%) as a white foam solid: m/z 408.1 (M+1).

Compound 63304:

To a solution of compound 44 (0.11 g, 0.27 mmol) in benzene (3 mL) was added DDQ (61 mg, 0.27 mmol). The solution was heated at 80° C. for 30 min. After cooling, the mixture was diluted with MTBE (50 mL), washed with sat. NaHCO₃ (20 mL), brine, dried over MgSO₄, and concentrated to give crude product as a light brown foam. The crude product was purified by column chromatography (0.5-1% EtOAc/CH₂Cl₂) to give product 63304 (20 mg, 18%) as a white foam solid: ¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 5.78 (br s, 1H), 5.68 (br s, 1H), 5.51 (br s, 1H), 4.00-3.85 (m, 4H), 2.88 (d, J=16 Hz, 1H), 2.82 (d, J=16 Hz, 1H), 2.71 (d, J=16 Hz, 1H), 2.61 (d, J=16 Hz, 1H), 2.22-2.15 (m, 1H), 2.05-1.97 (m, 1H), 1.90-1.40 (m, 9H), 1.30 (s, 3H), 1.33-1.22 (m, 2H), 0.86 (s, 3H); m/z 406.1 (M+1).

Compound 63311:

To a solution of compound 63304 (0.030 g, 0.074 mmol) in THF (5 mL) and water (1 mL) was added 1 N HCl (1 mL). The solution was stirred overnight and then allowed to stand for 72 h. The mixture was diluted with sat. NaHCO₃ (aq), and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give crude product. The crude product was purified by column chromatography (15% EtOAc/hexane) to give product 63311 (17 mg, 64%) as a white solid: ¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 5.80 (m, 1H), 5.73 (m, 1H), 5.53 (m, 1H), 2.91 (d, J=16 Hz, 1H), 2.84 (d, J=16 Hz, 1H), 2.74 (br d, J=16 Hz, 1H), 2.62 (br d, J=16 Hz, 1H), 2.50 (dd, J=19 and 9 Hz, 1H), 2.32 (dt, J=18 and 5 Hz, 1H), 2.13 (dt, J=19 and 9 Hz, 1H), 2.03-1.75 (m, 5H), 1.73-1.53 (m, 2H), 1.43-1.28 (m, 3H), 1.33 (s, 3H), 0.94 (s, 3H); m/z 362.0 (M+1).

Compound 45:

A solution of compound 43 (0.79 g, 2.07 mmol) in THF (25 mL) was placed under N₂ atmosphere. 5% Pd/C (100 mg) was added, and the mixture was evacuated and purged with H₂ (3×). The mixture was stirred under a H₂ balloon for 2 h, then filtered through a fine frit. The filtrate was concentrated and dried under vacuum to give compound 45 (0.78 g, 98%) as a white solid: m/z 385.1 (M+1).

Compound 46:

To a solution of di-isopropylamine (0.77 mL, 5.48 mmol) in THF (10 mL) at -78° C. was added n-BuLi (3.17 mL of a 1.6 M solution in hexane, 5.07 mmol). The solution was allowed to warm to 0° C. and stirred for 20 min, then re-cooled to -78° C. A solution of compound 45 (0.78 g, 2.03 mmol) in THF (10 mL) was added dropwise, and the solution was stirred 30 min. A solution of tosyl cyanide (0.44 g, 2.43 mmol) in THF (5 mL) was added dropwise, and the solution was stirred 30 min. Sat. NH₄Cl (aq) (10 mL) was added, and the mixture was allowed to warm to room temperature. The mixture was diluted with water (10 mL) and extracted with MTBE (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give crude product. The crude product was purified by column chromatography (15-20% EtOAc/hexane) to give compound 46 (0.46 g, 55%) as a white foam solid: m/z 410.1 (M+H).

Compound 63317:

A solution of compound 46 (0.34 g, 0.83 mmol) in DMF (3 mL) was cooled in an ice bath. 1,3-Dibromo-5,5-dimethylhydantoin (0.142 g, 0.50 mmol) was added, and the solution was stirred 2 h at 0° C. Pyridine (0.75 mL) was added, and the solution was heated at 55° C. for 21 h. After cooling, the

mixture was diluted with water (10 mL) and extracted with MTBE (2×30 mL). The combined organic extracts were washed with 0.5 M HCl (aq) (2×15 mL), sat. NaHCO₃ (aq) (20 mL), brine, dried over MgSO₄, concentrated, and dried under vacuum to give crude product. The crude product was purified by column chromatography (20% EtOAc/hexane) to give product 63317 (0.258 g, 76%) as a white foam solid: ¹H NMR (500 MHz, CDCl₃) δ 7.63 (s, 1H), 5.69 (br s, 1H), 3.98-3.83 (m, 4H), 2.28-2.12 (m, 2H), 2.10-1.96 (m, 2H), 1.94-1.40 (m, 15H), 1.35 (s, 3H), 1.34-1.20 (m, 2H), 0.91 (s, 3H); m/z 408.1 (M+1).

Compound 63318:

To a solution of 63317 (0.23 g, 0.56 mmol) in THF (10 mL) was added 0.5 N HCl (aq) (3 mL). The solution was stirred 50 h. The mixture was diluted with sat. NaHCO₃ (aq) and extracted with MTBE (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum at 50° C. to give product 63318 (200 mg, 98%) as a white foam solid: ¹H NMR (500 MHz, CDCl₃) δ 7.62 (s, 1H), 5.73 (br s, 1H), 2.50 (dd, J=19 and 9 Hz, 1H), 2.34 (dt, J=19 and 5 Hz, 1H), 2.22-2.02 (m, 2H), 2.01-1.55 (m, 15H), 1.38 (s, 3H), 1.38-1.24 (m, 2H), 0.94 (s, 3H); m/z 364.1 (M+1).

Compound 63329:

To a solution of compound 63318 (0.069 g, 0.19 mmol) in toluene (1 mL) and isopropanol (1 mL) was added aluminum tri-isopropoxide (58 mg, 0.28 mmol). The mixture was stirred at 75° C. for 20 h. The mixture was diluted with EtOAc (50 mL), washed with 1 N HCl (aq) (20 mL), sat. NaHCO₃ (aq) (20 mL), brine, dried over MgSO₄, and concentrated to give crude product. This crude product was combined with that from a previous run (0.082 mmol scale) and was purified by column chromatography (10-20% EtOAc/CH₂Cl₂) to give product 63329 (20 mg, 20%) as a white foam solid: ¹H NMR (500 MHz, CDCl₃) δ 7.61 (s, 1H), 5.71 (br s, 1H), 3.70 (br t, J=8 Hz, 1H), 2.29-2.06 (m, 3H), 1.98-1.13 (m, 18H), 1.38 (s, 3H), 1.08-0.97 (m, 1H), 0.83 (s, 3H); m/z 366.0 (M+1).

Compound 47:

A solution of acetyl chloride (0.125 mL) in 125 mL of methanol was treated with cholic acid (5 g, 0.012 mol) in one portion. The solution was stirred at room temperature for 72 h, at which time the solvent was concentrated in vacuo to give compound 47 (5.0 g, quantitative) as white solid: m/z 423.2 (M+1).

Compound 48:

Compound 47 (5.0 g, 0.0118 mol) was suspended in toluene (150 mL), followed by the addition of silver carbonate on celite (6.5 g) in one portion. The reaction mixture was refluxed for 3 hrs and then filtered hot through a sintered glass funnel. The filtrate was concentrated in vacuo giving a crude product. The crude product was taken up in CH₂Cl₂/THF (7:3) and passed through a pad of silica gel, eluting with CH₂Cl₂/THF (7:3), to give compound 48 (3.3 g, 66%) as a white solid: m/z 421.1 (M+1).

Compound 49:

Compound 48 (3.3 g, 7.85 mmol) was diluted with 25 mL of CH₂Cl₂, followed by the addition of diisopropylethylamine (3.3 mL) and chloromethyl methylether (1.89 g, 23.5 mmol), respectively. The solution was stirred at 45° C. for overnight (~14 h), cooled to room temperature, and was then concentrated to give a viscous liquid. This crude product was taken up in EtOAc (50 mL) and washed with a sat. KH₂PO₄ (aq) solution and brine. The organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated in vacuo to give crude product. The crude product was purified by column chromatography (elution with hexane/EtOAc 7:3) to

give compound 49 (2.8 g, 70%) as a viscous colorless liquid which solidified on standing: m/z 385.1 (M+1).

Compound 50:

Compound 49 (0.62 g, 1.21 mmol) was suspended in 9 mL of ethyl formate, followed by the dropwise addition of 30% sodium methoxide in methanol (0.5 mL). The reaction mixture was stirred at room temperature for approximately 2 h, at which time degassing was complete. To the reaction mixture was added 0.1 N HCl (aq) until the solution was at pH=3. Ethyl acetate (40 mL) and water (40 mL) were added, the organic phase was separated and dried over MgSO₄. The drying agent was filtered, and the filtrate was concentrated to give crude product. The crude product was purified by column chromatography (elution with hexane/EtOAc 7:3) to give product 50 (0.37 g) as a white solid: m/z 551.2 (M+1).

Compound 51:

Compound 50 (0.37 g, 0.67 mmol) was suspended in an ethanol/water solution (30 mL/5 mL), followed by the addition of hydroxylamine hydrochloride (0.12 g) in one portion. The solution was stirred at 60° C. for overnight (~14 h), cooled to room temperature, and concentrated in vacuo. The product was partitioned between CH₂Cl₂ (20 mL) and brine (20 mL). The organic phase was separated, dried over MgSO₄, then filtered, and the filtrate was concentrated to give crude product. The crude product was purified by column chromatography (elution with hexane/EtOAc 7:3) to give compound 51 (0.15 g, 40% from 49) as a viscous liquid: m/z 548.3 (M+1).

Compound 52:

Compound 51 (0.15 g, 0.27 mmol) was diluted with 1:1 THF/methanol (5 mL), followed by the dropwise addition of 30% sodium methoxide in methanol (0.5 mL). The reaction mixture was stirred at 55° C. for 2 hours, cooled to room temperature, and was then diluted with 1:1 EtOAc:1N HCl (aq) (40 mL). The organic phase was separated, dried (Na₂SO₄), filtered, and the filtrate was concentrated to dryness to give crude product. The crude product was purified by column chromatography (elution with hexane/EtOAc 7:3) to give compound 52 (0.060 g, 41%) as a white solid: m/z 440.1 (M+1).

Compound 63312:

Compound 52 (0.050 g, 0.093 mmol) was taken up in DMF (1 mL), followed by the addition of 1,3-dibromo-5,5-dimethylhydantoin (0.016 g, 0.055 mmol). The solution was stirred at room temperature for 3 hours, then treated with 0.25 mL of anhydrous pyridine. The solution was heated to 55° C. and was stirred at that temperature for 3 days. The solution was cooled to room temperature and diluted with EtOAc and 1 N HCl (aq) (25 mL each). The organic phase was separated, washed with water, and dried over sodium sulfate. The drying agent was filtered, and the filtrate was concentrated in vacuo to give crude product. The crude product was purified by column chromatography (gradient elution with hexane/EtOAc, from 7:3 to 1:1) to give product 63312 (0.040 g, 80%) as a white amorphous solid: ¹H NMR (500 MHz, CDCl₃) δ 7.55 (s, 1H), 4.70 (d, J=7 Hz, 1H), 4.67 (d, J=7 Hz, 1H), 4.64 (d, J=7 Hz, 1H), 4.56 (d, J=7 Hz, 1H), 3.77 (br s, 1H), 3.72 (br s, 1H), 3.66 (s, 3H), 3.48 (t, J=16 Hz, 1H), 3.39 (s, 3H), 3.30 (s, 3H), 2.45-2.31 (m, 2H), 2.23 (m, 1H), 2.15-2.02 (m, 2H), 1.92-1.53 (m, 11H), 1.44-1.23 (m, 2H), 1.25 (s, 3H), 1.08 (m, 1H), 0.92 (d, J=6 Hz, 3H), 0.73 (s, 3H); m/z 438, 408, and 376.

Compound 63314:

Compound 63312 (0.025 g, 0.047 mmol) was taken up in 2 mL of CH₂Cl₂ and then treated with 1 mL of 2 M HCl in diethyl ether. The solution was stirred at room temperature for overnight, then concentrated to dryness. The residue was was

purified by column chromatography (gradient elution with 7:3 to 1:1 hexane:EtOAc) to give product 63314 (0.010 g, 48%) as a viscous colorless liquid: ^1H NMR (500 MHz, CDCl_3) δ 7.52 (s, 1H), 4.06 (br s, 1H), 3.95 (br s, 1H), 3.59 (s, 3H), 3.54 (dd, J=17 and 15 Hz, 1H), 2.47 (dd, J=18 and 4 Hz, 1H), 2.26 (m, 1H), 2.10 (m, 1H), 2.03-1.53 (m, 14H), 1.50-1.13 (m, 4H), 1.27 (s, 3H), 1.00 (d, J=6 Hz, 3H), 0.76 (s, 3H); m/z 444.1 (M+1).

All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

- U.S. Pat. No. 5,443,826
- U.S. Pat. No. 5,599,795
- U.S. Pat. No. 6,025,395
- U.S. Pat. No. 6,326,507
- U.S. Pat. No. 6,974,801
- U.S. patent application Ser. No. 11/941,820
- U.S. patent application Ser. No. 12/352,473
- U.S. Provisional Application No. 61/046,332
- U.S. Provisional Application No. 61/046,342
- U.S. Provisional Application No. 61/046,352
- U.S. Provisional Application No. 61/046,366
- U.S. Provisional Application No. 61/111,333
- U.S. Provisional Application No. 61/111,269
- U.S. Provisional Application No. 61/111,294
- U.S. Patent Publication 2009/0060873
- U.S. Patent Application by Eric Anderson, Xin Jiang, Xiaofeng Liu; Melean Visnick, entitled "Antioxidant Inflammation Modulators: Oleanolic Acid Derivatives With Saturation in the C-Ring," filed Apr. 20, 2009.
- U.S. Patent Application by Eric Anderson, Xin Jiang and Melean Visnick, entitled "Antioxidant Inflammation Modulators: Oleanolic Acid Derivatives with Amino and Other Modifications At C-17," filed Apr. 20, 2009.
- U.S. Patent Application by Xin Jiang, Jack Greiner, Lester L. Maravetz, Stephen S. Szucs, Melean Visnick, entitled "Antioxidant Inflammation Modulators: Novel Derivatives of Oleanolic Acid," filed Apr. 20, 2009.
- U.S. Patent Application by Xin Jiang, Xiaofeng Liu, Jack Greiner, Stephen S. Szucs, Melean Visnick, entitled, "Antioxidant Inflammation Modulators: C-17 Homologated Oleanolic Acid Derivatives," filed Apr. 20, 2009.
- Abraham and Kappas, *Free Radic. Biol. Med.*, 39(1):1-25, 2005.
- Akiyama et al., *Alzheimer Dis. Assoc. Disord.*, 14(1):547-53, 2000.
- Angulo et al., *Eur. J. Immunol.*, 30:1263-1271, 2000.
- Araujo et al., *J. Immunol.*, 171(3):1572-1580, 2003.

- Arend and Dayer, *Arthritis Rheum.*, 38:151-160, 1995.
- Arend et al., *Annu. Rev. Immunol.*, 16:27-55, 1998.
- Autenrieth et al., *Infect. Immun.*, 62:2590-2599, 1994.
- Bach, *Hum. Immunol.*, 67(6):430-432, 2006
- 5 Bagasra et al., *Proc. Natl. Acad. Sci. USA*, 92:12041-12045, 1995.
- Ball, *Ann. Rheum. Dis.*, 30:213-223, 1971.
- Barton et al., *J. Chem. Soc. Perkin Trans. I.*, 2209, 1980.
- Beal, *Curr. Opin. Neurobiol.*, 6:661-666, 1996.
- 10 Bendzen et al., *Scand. J. Rheumatol.*, 28:599-606, 1988.
- Blanchette et al., *Tetrahedron Lett.*, 25:2183, 1984.
- Blumberg et al., *Arthritis Rheum.*, 7:93-97, 1964.
- Botoman et al., *Am. Fam. Physician*, 57(1):57-68, 1998.
- Brandt et al., *Arthritis Rheum.*, 43:1346-1352, 2000.
- 15 Braun et al., *Arthritis Rheum.*, 42:2039-2044, 1999.
- Brewerton et al., *Lancet*, 1:904-907, 1973a.
- Brewerton et al., *Lancet*, 1:956-957, 1973b.
- Bronte et al., *Trends Immunol.*, 24:302-306, 2003.
- Brown and DuBois, *J. Clin. Oncol.*, 23:2840-2855, 2005.
- 20 Brynskov et al., *N. Engl. J. Med.*, 321(13):845-850, 1989.
- Burger and Dayer, *Neurology*, 45(65-6):539-43, 1995.
- Cai et al., *Nat. Med.*, 11(2):183-190, 2005.
- Calin and Taurog, In: *The Spondylarthritides*, Calin et al. (Eds.), Oxford, UK. Oxford University Press, 179, 1998.
- 25 Cann et al., *Gut*, 24(12):1135-1140, 1983.
- Cardona et al., *Tetrahedron*, 42:2725, 1986.
- Chauhan and Chauhan, *Pathophysiology*, 13(3):171-181 2006.
- Chomarat et al., *Arthritis Rheum.*, 38:1046-1054, 1995.
- 30 Coyle and Puttfarcken, *Science*, 262:689-695, 1993.
- Crowell et al., *Mol. Cancer Ther.*, 2:815-823, 2003.
- Culver et al., *Science*, 256:1550-1552, 1992.
- Danishefsky et al., *J. Am. Chem. Soc.*, 101:6996, 1979.
- de Waal et al., *J. Exp. Med.*, 174:1209-1220, 1991.
- 35 Dickerson et al., *Prog Neuropsychopharmacol Biol. Psychiatry*, Mar. 6, 2007.
- Dinarello, *Int. Rev. Immunol.*, 16:457-499, 1998.
- Dionne et al., *Clin. Exp. Immunol.*, 112(3):435-442, 1998.
- Doran et al., *J. Rheumatol.*, 30(2):316-320, 2003.
- 40 Drossman et al., *Dig. Dis. Sci.*, 38(9):1569-1580, 1993.
- Drossman et al., *Gastroenterol.*, 112(6):2120-2137, 1997.
- Dudhgaonkar et al., *Eur. J. Pain*, 10(7):573-9, 2006.
- Eikelenboom et al., *Glia*, 40(2):232-239, 2002.
- Ettehad et al., *Clin. Exp. Immunol.*, 96(1):146-151, 1994.
- 45 Everhart et al., *Gastroenterol.*, 100(4):998-1005, 1991.
- Fearon and Locksley, *Science*, 272(5258):50-53, 1996.
- Feldtkeller et al., *Rheumatol. Int.*, 23(2):61-66, 2003.
- Firestein et al., *Arthritis Rheum.*, 37:644-652, 1994.
- Forstermann, *Biol. Chem.*, 387:1521, 2006.
- 50 Fujikawa et al., *Ann. Rheum. Dis.*, 54:318-320, 1995.
- Funakoshi et al., *Digestion*, 59(1):73-78, 1998.
- Galley and Webster, *Br. J. Anaesth.*, 77:11-16, 1996.
- Gehrmann et al., *Glia*, 15(2):141-151, 1995.
- Genain and Nauser, *J. Mol. Med.*, 75:187-197, 1997.
- 55 Gladman et al., *Br. J. Rheumatol.*, 22:675-679, 1995.
- Gladman et al., *J. Med.*, 62:127-141, 1987.
- Gladman, *Rheum. Dis. Clin. North Am.*, 18:247-256, 1992.
- Goodman et al., *Kidney Int.*, 72(8):945-953, 2007.
- Graeber et al., *Glia*, 40(2):252-259, 2002.
- 60 Greten et al., *Cell*, 118:285-296, 2004.
- Griffin et al., *Proc. Natl. Acad. Sci. USA*, 86(19):7611-7615, 1989.
- Guilherme et al., *Nat. Rev. Mol. Cell Biol.*, 9(5):367-77, 2008.
- Gwee et al., *Gut*, 44(3):400-406, 1999.
- 65 Hahn and Tsao, In: *Dubois' Lupus Erythematosus*, 4th Ed, Wallace and Hahn (Eds.), Lea and Febiger, Philadelphia, 195-201, 1993.

Handbook of Pharmaceutical Salts: Properties, Selection and Use (Stahl & Wermuth, Eds.), Verlag Helvetica Chimica Acta, 2002.

- Hannum et al., *Nature*, 343:336-340, 1990.
 Hanson et al., *BMC Medical Genetics*, 6(7), 2005.
 Hansson et al., *Annu. Rev. Pathol. Mech. Dis.*, 1:297-329, 2006.
 Harrison and Symmons et al., *Ann. Rheum. Dis.*, 57(6):375-377, 1998.
 Harrison et al., *J. Rheumatol.*, 25(12):2324-2330, 1998.
 Hart et al., *Immunology*, 84:536-542, 1995.
 Hohler et al., *Arthritis Rheum.*, 41:1489-1492, 1998.
 Hohler et al., *J. Invest. Dermatol.*, 109:562-565, 1997.
 Honda et al., *Bioorg. Med. Chem. Lett.*, 12:1027-1030, 2002.
 Honda et al., *Bioorg. Med. Chem. Lett.*, 19:2711-2714, 1998.
 Honda et al., *Bioorg. Med. Chem. Lett.*, 9:3429-3434, 1999.
 Honda et al., *J. Med. Chem.*, 43:1866-1877, 2000a.
 Honda et al., *J. Med. Chem.*, 43:4233-4246, 2000b.
 Horwitz and Fisher, *N. Engl. J. Med.*, 344(24):1846-1850, 2001.
 Hotamisligil, *Nature*, 444(7121):860-7, 2006.
 Ishikawa et al., *Circulation*, 104(15):1831-1836, 2001.
 Ishizawa and Dickson, *J. Neuropathol. Exp. Neurol.*, 60(6):647-657, 2001.
 Jacob et al., *Proc. Natl. Acad. Sci. USA*, 87:1233-1237, 1990.
 Jailwala et al., *Ann. Intern. Med.*, 133(2):136-147, 2000.
 Jarvis, *Curr. Opin. Rheumatol.*, 10(5):459-467, 1998.
 Jarvis, *Pediatr. Ann.*, 31(7):437-446, 2002.
 Jones et al., *Br. J. Rheumatol.*, 33(9):834-839, 1994.
 Jonsson et al., *Br. J. Rheumatol.*, 32(7):578-581, 1993.
 Jonsson et al., *Oral Dis.*, 8(3):130-140, 2002.
 Jonsson et al., *Trends Immunol.*, 22(12):653-654, 2001.
 Kahle et al., *Ann. Rheum. Dis.*, 51:731-734, 1992.
 Kahne and Collum, *Tetrahedron Lett.*, 22:5011, 1981.
 Kaltschmidt et al., *Proc. Natl. Acad. Sci. USA*, 94:2642-2647, 1997.
 Kawakami et al., *Brain Dev.*, 28(4):243-246, 2006.
 Kellow and Phillips, *Gastroenterol.*, 92(6):1885-1893, 1987.
 Kendall-Tackett, *Trauma Violence Abuse*, 8(2):117-126, 2007.
 Khan et al., *J. Neurochem.*, 71:78-87, 1998.
 Khan et al., *Toxicol. Applied Pharmacol.*, 103:482-490, 1990.
 Kortylewski et al., *Nat. Med.*, 11:1314-1321, 2005.
 Kotake et al., *Infect. Immun.*, 67:2682-2686, 1999.
 Kotzin and O'Dell, In: *Samler's Immunologic Diseases*, 5th Ed., Frank et al. (Eds.), Little Brown & Co., Boston, 667-697, 1995.
 Kotzin, *Cell*, 85:303-306, 1996.
 Kruger et al., *J. Pharmacol. Exp. Ther.*, 319(3):1144-1152, 2006.
 Kuboyama, *Kurume Med. J.*, 45(1):33-37, 1998.
 Lahesmaa et al., *J. Immunol.*, 148:3079-3085, 1992.
 Lee et al., *Glia.*, 55(7):712-22, 2007.
 Lencz et al., *Mol. Psychiatry*, 12(6):572-80, 2007.
 Lipsky, In: *Harrison's principles of internal medicine*, Fauci et al., (Eds.), 14th Ed., NY, McGraw-Hill, 1880-1888, 1998.
 Liu et al., *FASEB J.*, 20(2):207-216, 2006.
 Lo et al., *Curr. Dir. Autoimmun.*, 1:226-246, 1999.
 Luger et al., *Ital. J. Gastroenterol. Hepatol.*, 30(3):338-344, 1998.
 Lynn and Friedman, *N. Engl. J. Med.*, 329(26):1940-1945, 1993.
 Macatonia et al., *J. Immunol.*, 150:3755-3765, 1993.
 March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (March's Advanced Organic Chemistry), Smith and March (Eds.), 2007.

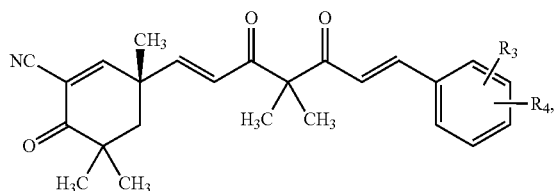
- Marsal et al., *Rheumatology*, 38:332-337, 1999.
 Mazur et al., *Cell Microbiol.*, 9(7):1683-94, 2007.
 Mazzoni et al., *J. Immunol.*, 168:689-695, 2002.
 McAlindon et al., *Gut*, 42(2):214-219, 1998.
 5 McGeer and McGeer, *Brain Res. Brain Res. Rev.*, 21:195-218, 1995.
 McGeer et al., *Neurology*, 19:331-338, 1996.
 McGonagle et al., *Arthritis Rheum.*, 41:694-700, 1998.
 McGonagle et al., *Curr. Opin. Rheumatol.*, 11:244-250, 1999.
 10 McIver et al., *Pain*, 120(1-2):161-9, 2005.
 Mease et al., *Lancet*, 356:385-390, 2000.
 Merrill and Benvenist, *Trends Neurosci.*, 19:331-338, 1996.
 Mertz et al., *Gastroenterol.*, 118(5):842-848, 2000.
 Moll and Wright, *Ann. Rheum. Dis.*, 32:181-201, 1973.
 15 Moll and Wright, *Semin. Arthritis Rheum.*, 3:55-78, 1973.
 Morris et al., *J. Mol. Med.*, 80(2):96-104, 2002.
 Morse and Choi, *Am. J. Respir. Crit. Care Med.*, 172(6):660-670, 2005.
 Morse and Choi, *Am. J. Respir. Crit. Care Med.*, 27(1):8-16, 2002.
 20 Nath et al., *Neurology*, 66(1):149-150, 2006.
 Neal et al., *BMJ*, 314(7083):779-782, 1997.
 Nichols, *Drug News Perspect.*, 17(2):99-104, 2004.
 Nielen et al., *Arthritis Rheum.*, 50(2):380-386, 2004.
 Ohnishi et al., *Int. Immunol.*, 6:817-830, 1994.
 Pall, *Med. Hypoth.*, 69:821-825, 2007.
 Partsch et al., *Br. J. Rheumatol.*, 24:518-523, 1997.
 Pica et al., *Antimicrob. Agents Chemother.*, 44(1):200-4, 2000.
 30 Pimentel et al., *Am. J. Gastroenterol.*, 95(12):3503-3506, 2000.
 Pociot et al., *Scand. J. Immunol.*, 42(4):501-504, 1995.
 Prieur et al., *Lancet*, 2:1240-1242, 1987.
 Rajakariar et al., *Proc. Natl. Acad. Sci. USA*, 104(52):20979-84, 2007.
 Rantapaa-Dahlqvist et al., *Arthritis Rheum.*, 48(10):2741-2749, 2003.
 Rasmusson et al., *J. Med. Chem.*, 29:2298, 1986.
 Reimund et al., *Eur. J. Clin. Invest.*, 28(2):145-150, 1998.
 40 Ribbens et al., *Eur. Cytokine Netw.*, 11:669-676, 2000.
 Rogers et al., *Neurobiol. Aging*, 9(4):339-349, 1988.
 Rogler and Andus, *World J. Surg.*, 22(4):382-389, 1998.
 Rooney et al., *Rheumatol. Int.*, 10:217-219, 1990.
 Ross et al., *Nutr. Neurosci.*, 6(5):277-81, 2003.
 45 Rostom et al., *Ann. Intern. Med.*, 146, 376-389, 2007.
 Rostheim, *Med. Clin. North Am.*, 84(5):1247-1257, 2000.
 Roush et al., *Cancer*, 54(3):596-601, 1984.
 Ruster et al., *Scand. J. Rheumatol.*, 34(6):460-3, 2005.
 Sacerdoti et al., *Curr. Neurovasc. Res.*, 2(2):103-111, 2005.
 50 Saiki et al., *Scand. J. Gastroenterol.*, 33(6):616-622, 1998.
 Salomonsson and Jonsson, *Arthritis Rheum.*, 48(11):3187-3201, 2003.
 Salomonsson et al., *Scand. J. Immunol.*, 55(4):336-342, 2002.
 55 Salvarani et al., *Curr. Opin. Rheumatol.*, 1998; 10:299-305, 1998.
 Salvemini et al., *J. Clin. Invest.*, 93:1940-1947, 1994.
 Sandler, *Gastroenterol.*, 99(2):409-415, 1990.
 Sarchielli et al., *Cephalalgia*, 26(9):1071-1079, 2006.
 60 Satoh et al., *Proc. Natl. Acad. Sci. USA*, 103(3):768-773, 2006.
 Schellekens et al., *Arthritis Rheum.*, 43(1):155-163, 2000.
 Schlaak et al., *Clin. Exp. Rheumatol.*, 14:155-162, 1996.
 Schlaak et al., *Eur. J. Immunol.*, 22:2771-2776, 1992.
 Schlosstein et al., *NE J. Medicine*, 288:704-706, 1973.
 Schreiber, *Neth. J. Med.*, 53(6):524-31, 1998.
 Schulz et al., *Antioxid. Redox. Sig.*, 10:115, 2008.

105

- Sieper and Braun, *Arthritis Rheum.*, 38:1547-1554, 1995.
 Simon et al., *Clin. Exp. Immunol.*, 94:122-126, 1993.
 Simon et al., *Proc. Natl. Acad. Sci. USA*, 91:8562-85666, 1994.
 Simonian and Coyle, *Annu. Rev. Pharmacol. Toxicol.*, 36:83-106, 1996.
 Sinha et al., *Cancer Res.*, 67:4507-4513, 2007.
 Stack et al., *Lancet*, 349(9051):521-524, 1997.
 Stewart et al., *Neurology*, 48:626-632, 1997.
 Strejan et al., *J. Neuroimmunol.*, 7:27, 1984.
 Szabo et al., *Nature Rev. Drug Disc.*, 6:662-680, 2007.
 Takahashi et al., *Cancer Res.*, 57:1233-1237, 1997.
 Talley et al., *Gastroenterol.*, 109(6):1736-1741, 1995.
 Tamer and Tannenbaum, *Biochim. Biophys. Acta.*, 1288:F31-F36, 1996.
 Targan et al., *N. Engl. J. Med.*, 337(15):1029-1035, 1997.
 Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670.
 Touzani et al., *J. Neuroimmunol.*, 100(1-2):203-215, 1999.
 Tumlin et al., *Am. J. Cardiol.*, 98(6A):14K-20K, 2006.
 Vazquez et al., *J. Virol.*, 79(7):4479-91, 2005.
 van den Berg, *Semin. Arthritis Rheum.*, 30(55-2):7-16, 2001.
 van Dullemen et al., *Gastroenterol.*, 109(1):129-135, 1995.
 van Hozegand and Verspaget, *Drugs*, 56(3):299-305, 1998.
 Vodovotz et al., In: *Handbook of Experimental Immunology*, Volumes I-IV, 1996.
 Wardle, *Nephrol. Dial. Transplant.*, 16(9):1764-8, 2001.
 Warrington et al., *Arthritis and Rheumatism*, 44:13-20, 2001.
 Weyand and Goronzy, *Ann. NY Acad. Sci.*, 987:140-149, 2003.
 Whitehead et al., *Gastroenterol.*, 98(5 Pt 1):1187-1192, 1990.
 Williams et al., *Clin. Neurosci.*, 2(3-4):229-245, 1994.
 Wordsworth, In: *Genes and Arthritis*, Brit. Medical Bulletin, 51:249-266, 1995.
 Wright, *Ann. Rheum. Dis.*, 15:348-356, 1956.
 Wright, *Clin. Orthop. Related Res.*, 143:8-14, 1979.
 Wu et al., *Tetrahedron*, 63:5036, 2007.
 Xanthou et al., *Arthritis Rheum.*, 44(2):408-418, 2001.
 Yates et al., *Cancer Res.*, 66(4): 2488-2494, 2006.
 Yin et al., *Arthritis Rheum.*, 40:1788-1797, 1997.
 Yin et al., *Rheumatology*, 38:1058-1067, 1999.
 Yoh et al., *Kidney Int.*, 60(4):1343-1353, 2001.
 Yu et al., *Nat. Rev. Immunol.*, 7:41-51, 2007.
 Zhou et al., *Am. J. Pathol.*, 166(1):27-37, 2005.
 Zhou et al., *Cancer Sci.*, 98:882-889, 2007.
 Zingarelli et al., *J. Immunol.*, 171(12):6827-6837, 2003.

What is claimed is:

1. A compound of the formula:



wherein:

R_3 and R_4 are each independently:

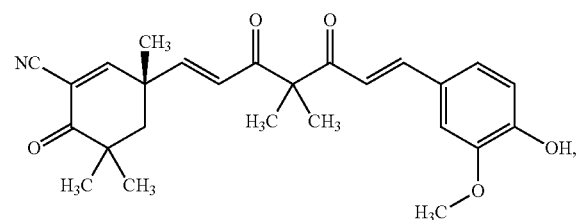
hydrogen, hydroxy, halo, amino, hydroxyamino, nitro, cyano, azido, or mercapto; or

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alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heteroaralkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkenyloxy_(C≤12), alkynyloxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), heteroaralkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), alkoxyamino_(C≤12), alkenylamino_(C≤12), alkynylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), heteroaralkylamino_(C≤12), amido_(C≤12), alkylsulfonylamino_(C≤12), alkylsilyl_(C≤12), alkylsilyloxy_(C≤12), or a substituted version of any of these groups;

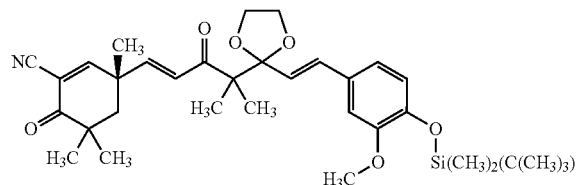
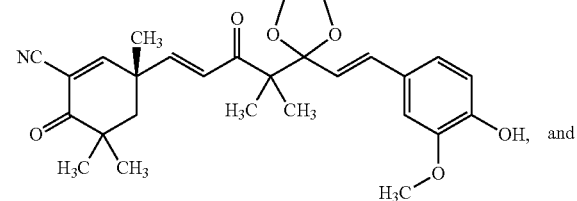
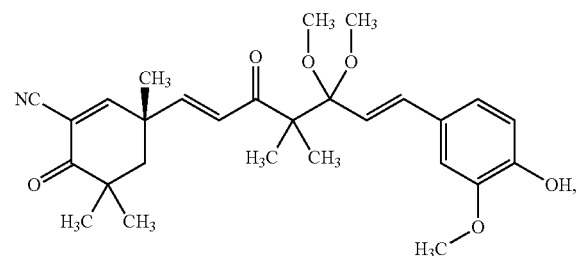
or a pharmaceutically acceptable salt, tautomer, acetal, or ketal, thereof.

2. The compound of claim 1, further defined by the formula:



or a pharmaceutically acceptable salt, ketal, or tautomer thereof.

3. The compound of claim 1, further selected from the group consisting of:



or a pharmaceutically acceptable salt, ketal, or tautomer thereof.

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